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(54) Use of biphosphonate squalene synthetase inhibitors in pharmaceutical compositions useful in lowering cholesterol.

(57) The present invention relates to the use of a bisphosphonate squalene synthetase inhibitor for the preparation of a pharmaceutical composition useful in inhibiting cholesterol biosynthesis by inhibiting de novo squalene production.

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The present invention relates to the use of a bisphosphonate squalene synthetase inhibitor for the preparation of a pharmaceutical composition useful in inhibiting cholesterol biosynthesis by inhibiting de novo squalene production.

Squalene synthetase is a microsomal enzyme which catalyzes the reductive dimerization of two molecules of farnesyl pyrophosphate (FPP) in the presence of nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) to form squalene (Poulter, C. D.; Rilling, H. C., "Biosynthesis of Isoprenoid Compounds", Vol. I, Chapter 8, pp. 413-441, J. Wiley and Sons, 1981 and references therein). This enzyme is the first committed step of the de novo cholesterol biosynthetic pathway. The selective inhibition of this step should allow the essential pathways to isopentenyl tRNA, ubiquinone, and dolichol to proceed unimpeded. Squalene synthetase, along with HMG-CoA reductase has been shown to be down-regulated by receptor mediated LDL uptake (Faust, J. R.; Goldstein, J. L.; Brown, M. S. Proc. Nat. Acad. Sci. USA, 1979, 76, 5018-5022), lending credence to the proposal that inhibiting squalene synthetase will lead to an up-regulation of LDL receptor levels, as has been demonstrated for HMG-CoA reductase, and thus ultimately should be useful for the treatment and prevention of hypercholesterolemia and atherosclerosis.

In accordance with the present invention, pharmaceutical compositions are provided for inhibiting cholesterol biosynthesis employing a bisphosphonate squalene synthetase inhibitor which includes a methylene bridge between the phosphonate moities and includes at least one lipophilic group attached to the methylene group which bridges the phosphonate moieties.

As will be seen hereinafter, the terms "bisphosphonic," "diphosphonic," "bisphosphonates" and "diphosphonates" are used interchangeably.

The term "lipophilic group" refers to a group which preferably contains at least six carbons (more preferably greater than 10) and preferably less than 2 polar substituents bearing OH, NH or C = O functions. The lipophilic substituent is required for strong enzyme inhibitor binding and inhibition of the enzyme squalene synthetase or other enzymes in the cholesterol biosynthetic pathway such as in the pathway from isopentenyl diphosphate to squalene, that is, farnesyl diphosphate synthetase and isopentenyl diphosphate - dimethylallyl diphosphate isomerase.

According to one aspect of the present invention, pharmaceutical compositions are provided for inhibiting or treating hypercholesterolemia, and thereby inhibiting or treating atherosclerosis, by administering to a patient in need of such treatment a squalene synthetase inhibiting amount of a bisphosphonate compound having the structure

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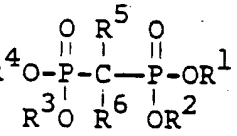
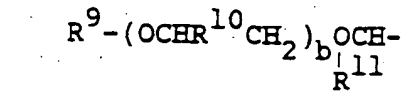
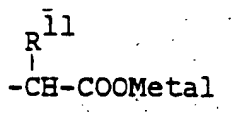


wherein R^1, R^2, R^3 and R^4 are the same or different and are H, alkyl, aryl, alkylaryl, arylalkyl, ammonium, alkali metal or a prodrug ester, preferably no more than one of R^1, R^2, R^3 and R^4 is alkyl, wherein at least one of R^5 and R^6 is a hydrocarbyl group having at least 6 carbons (such as alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, arylalkenyl); heterocyclic (such as succinimdyl, pyridyl, quinalyl, morpholino, furanyl, indolyl, picolinyl, thiophene, imidazole, oxazole, isoxazole, thiazole, pyridine, 1,2,3-triazole, 1,2,4-triazole, benzimidazole, tetrahydrofuranyl, pyrrolidino, piperidino, 5-membered heteroarylmethyl containing 2 to 4 N atoms or 1-2 N atoms plus an O or S atom); heterocyclicalkyl (wherein heterocyclic is as defined above such as 1-(decahydroquinolin-3-yl)methane); amino; alkylamino; dialkylamino; arylalkylaminoalkyl; ethylcarbonyloxymethylamino; cycloalkyl(alkyl)amino; alkenylamino, cycloalkylamino, aminocycloalkyl; aminocycloalkylalkyl; N-hydroxy-N-ethylamino; acetylamino; aminoalkyloxyalkyl; (benzo-or cyclohexeno-fused) 5 membered heteroaryl containing 2-4 N atoms or 1-2 Natoms plus an O or S atom; R^8-X-$(CH_2)_a$- (wherein R^8 is H, alkyl, or a nitrogen containing 6-membered aromatic ring such as pyridyl, indanyl, hexahydroindanyl or picolyl; X is O, NH or a single bond and a is 0 to 7);



(wherein R^9 is C_1-C_{10} alkyl, optionally substituted aryl, phenylalkyl or naphthylalkyl),



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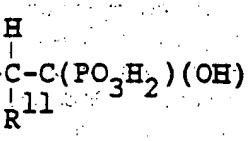
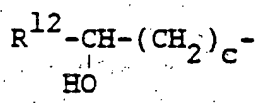
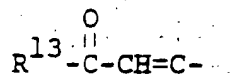


(wherein R^{10} and and R^{11} are the same or different and are H or methyl, b is 1 to 20));



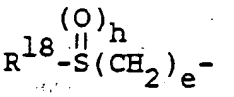
(wherein R^{12} is H, phenyl or phenyl substituted with halogen, alkyl or hydroxy and c is 0 to 9);



(wherein R^{13} is tert-alkyl ($CR^{14}R^{15}R^{16}$ wherein R^{14} and R^{15} are independently C_1-C_3 alkyl and R^{16} is C_1-C_{10} alkyl), cycloalkyl, aryl or heteroaryl; or substituted cycloalkyl, substituted aryl or substituted heteroaryl wherein the substituent is halogen, C_1-C_4 alkyl, alkoxy or dialkylamino);

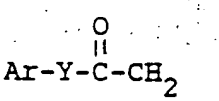
4-Cl-C_6H_5-S-CH_2; aryloxy;

R^{17}-$(QCH_2CH_2)_dO$- (wherein R^{17} is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, aryl or arylalkyl, or each of the above R^{17} groups optionally substituted with C_1-C_4 alkyl, amino, alkylamino, carboxyl, alkoxycarbonyl, hydroxy, alkoxy, phenoxy, mercapto, alkylthio, phenylthio, halogen or trifluoromethyl, Q is O or S and d is 0, 1 or 2);



(wherein e is 0 to 10, h is 0, 1 or 2, R^{18} is H, cycloalkyl, aryl, alkyl, each optionally substituted with OH, SH, halogen, alkoxycarbonyl or NZ_1Z_2, phenyl optionally substituted with halogen, nitro, lower alkyl, alkoxy, trifluoromethyl, amino, carboxyl, CO_2alkyl, -$CONZ_1Z_2$, -$CSNZ_1Z_2$, a 5- or 6-membered heterocyclic radical containing 1 or 2 heteroatoms, which are N or S, which may or may not be fused to a benzene ring, Z_1 and Z_2 are independently H or lower alkyl);

thiol; phenylthio; chlorophenylthio; 4-thiomorpholinyl;

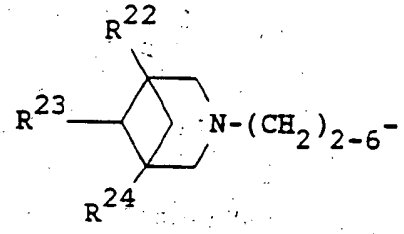


(wherein Ar is aryl, pyrrolyl or aryl optionally substituted with C_1-C_4 alkyl, alkoxy, halo (F, Cl), naphthyl, biphenyl or thienyl and Y is NH or a single bond);

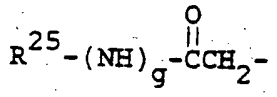
$R^{19}SCH_2$- (wherein R^{19} is alkyl, aryl or arylalkyl);

A-$(CH_2)_f$-NH- (wherein A is C_5-C_8 cycloalkenyl, bicycloheptyl, bicycloheptenyl, saturated C_4-C_7

heterocycle containing O,S,SO or SO_2);



(wherein R^{22} is H, C_1-C_{20}alkyl, alkoxy, aryl, R^{23} is H, C_1-C_{20}alkyl, alkoxy, aryl, halo, carboxyl, R^{24} is H, C_1-C_{20} alkyl, alkoxy);

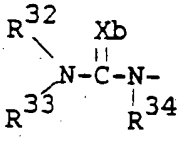


(wherein R^{25} is (alkyl-substituted)pyrrolyl or phenyl and g is 0 or 1);

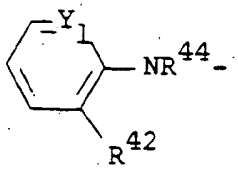
aromatic-substituted mono- or biazacyclylalkyl (alkyl group bonds with the N in the heterocycle) (such as 3-(4-phenylpiperidino)propyl);

R^{31}-Ax-CO-CH_2-

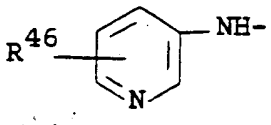
(wherein Ax is phenyl, naphthyl, mono- or bicyclic-N-containing heterocycle and R^{31} is H, halo, lower alkyl or lower alkoxy);



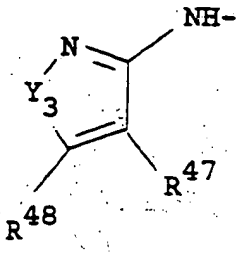
(wherein R^{32} is aryl, aralkyl, alkyl, R^{33} is H or aryl, Xb is O or S, and R^{34} is H or alkyl);



(wherein R^{42} is H, alkyl or halo, Y_1 is N, NO, or $NR^{43}Y_2$ wherein R^{43} is alkyl and Y_2 is halo; and R^{44} is H or aliphatic acyl);



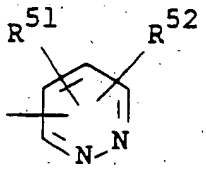
(wherein R^{46} is H, halo or alkyl);

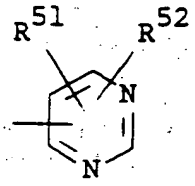


(wherein Y_3 is O or NH, R^{47} is H, alkyl or halo, and R^{48} is H or alkyl);

R^{50}-NH-

(wherein R^{50} is





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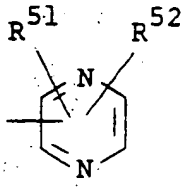
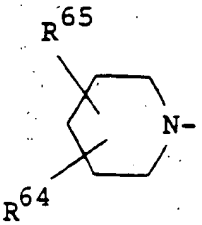
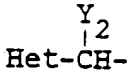


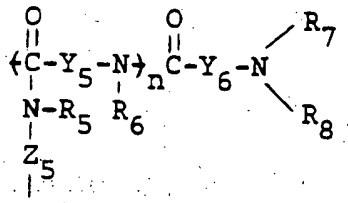
wherein R^{51} and R^{52} are H, halo, alkyl or hydroxy);



(wherein R^{64} is alkyl and R^{65} is H or alkyl;



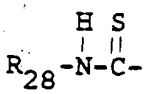
wherein Het is a heteroaromatic 5-membered ring with 2 or 3 heteroatoms, optionally partially hydrogenated and optionally substituted by one or more alkyl, alkoxy, phenyl, cyclohexyl, cyclohexylmethyl, halo or amino, with 2 adjacent alkyl optionally together forming a ring (Het cannot be pyrazole), and Y_2 is H or lower alkyl);



(wherein Y_4 is H or OH, R_5-R_8 are independently H or lower alkyl, whereby R_7 and Y_6 or R_6 and Y_5 or R_5 and Z_5, together with the nitrogen atom to which they are attached can form a 5- or 6-membered ring, Y_6 and Y_5 which can be the same or different are C_1-C_6 alkylene chains optionally substituted by aromatic or heteroaromatic radicals, Z_5 is C_1 to C_6 alkylene which can include heteroatoms and optionally substituted by aromatic or heteroaromatic, n is 0, 1 or 2;

R_{27}-Z_9-

(wherein R_{27} is aryl or heterocyclyl both optionally substituted by one or more of lower alkyl, lower alkoxy, lower alkylthio, halo(lower)alkyl, acyl, acylamino or halo, or R_{27} is lower alkyl substituted by heterocyclyl which is optionally substituted by acyl); R_{27}-Z_9 is R_{27}-NHC(=X_9), R_{27}-C(=O)NH-, R_{27}-SO_2-NH- (wherein X_9 is O or S);



(wherein R_{28} is phenyl, pyridyl or quinolyl substituted by lower alkylsulphonylamino, halo-lower alkylsulphonylamino, arylsulphonylamino and mono- or di-lower alkylamino);

R_{29}-CO-[-$R_{30}(CH_2)_o$CO-]$_p$-NH-

(wherein R_{29}-CO- is a residue of a pharmaceutically active compound R_{29}-COOH, wherein R_{29} is an anti-inflamatory agent, or antioncotic agent or hormone ,

R_{30} is -NH- or -O-

p is 0 or 1;

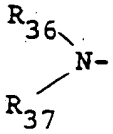
o is 1-10);

R_{33}-$(CH_2)_q$-

(wherein R_{33} is an N-bonded azabicycloalkyl group with 3 to 8-membered rings and q is 2 to 4);

R_{34}-$(CH_2)_r$-

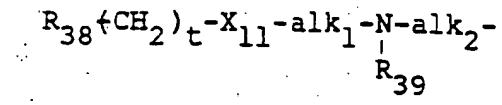
(wherein R_{34} is an N-bonded, aryl-substituted mono-or diazacycloaliphatic group);



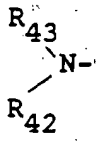
(wherein R_{36} is 5 membered heteroaryl with 2-4 N or with 1-2 N plus an O or S atom, optionally fused to a benzo or cyclohexeno ring;

R_{36} can be C substituted by lower alkyl, phenyl (optionally substituted by lower alkyl, alkoxy and/or halo), lower alkoxy, OH, di(lower alkyl)amino, lower alkylthio and/or halo, and/or N substituted by lower alkyl or phenyl (lower) alkyl (optionally substituted by lower alkyl, lower alkoxy and/or halo);

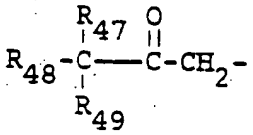
R_{37} is H or lower alkyl; provided R_{37} is not H if R_{36} is optionally substituted alkyl and/or halo substituted 3-pyrazolyl or 3-isoxazolyl);



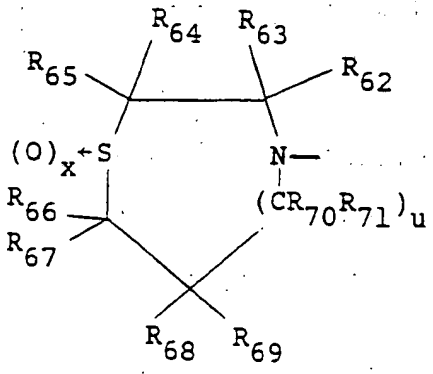
(wherein R_{38} is aromatic residue;
t is 0-3;
X_{11} is 0 S (optionally oxidized) or imino (optionally substituted by aliphatic group);
alk_1 and alk_2 are divalent aliphatic groups;
R_{39} is H or monovalent aliphatic group);



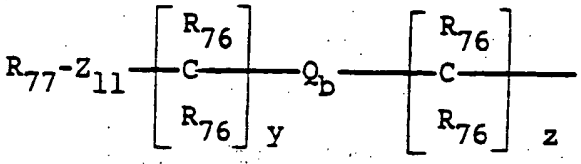
(wherein R_{42} and R_{43} are hydrogen, alkyl having one to 22 carbon atoms, cycloalkyl having five to six carbon atoms, phenyl alkylphenyl having seven to 18 carbon atoms, phenylalkyl having seven to 18 carbon atoms and together with the nitrogen atom, piperidino, pyrrolidino and morpholino);



(wherein R_{47} is optionally branched C_1-C_8 alkyl,
R_{48} and R_{49} are each methyl or ethyl, and
M is H or a cation of a water-soluble base);



(wherein R_{62}-R_{71} is H, straight, branched or alicyclic 1-10C hydrocarbyl, aryl or aryl-(1-4C)-alkyl;
x is 0 or 1;
u is 0, 1 or 2;
or R_{62} and R_{64} may complete a 5- to 7-membered saturated aliphatic ring optionally substituted by 1 or more alkyl groups);



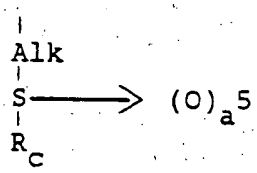
(wherein Z_{11} is an N-containing 6-membered ring heterocycle moiety selected from piperidinyl, diazinyl or triazinyl;

Q_b is a covalent bond, O, S or NR_{76};

y, z, and y + z are integers of 0-10;

R_{76} is H, or C_1-C_3alkyl;

R_{77} is one or more substituted selected from H, halogen, 1-3C alkyl, unsubstituted amino and its amide derived from a 1-3C carboxylic acid, mono(1-3C alkyl) amino and its amide derived from a 1-3C carboxylic acid, di(1-3C alkyl)amino, tri(1-3C alkyl) ammonium, hydroxy or its ester derived from a 1-3C carboxylic acid, ether having 1-3C, CO_2H and its salts and esters derived from 1-3C alcohols, its amide optionally substituted with one or two 1-3C alkyl groups, and NO_2);



(wherein R_c represents:

C_1-C_6 alkyl group,

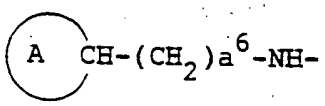
C_5-C_7 cycloalkyl group,

phenyl group optionally monosubstituted or polysubstituted by a halogen, a C_1-C_6 alkyl group or a trifluoromethyl group, or

5-membered or 6-membered heterocycle containing 1 or 2 heteroatoms chosen from nitrogen and sulfur,

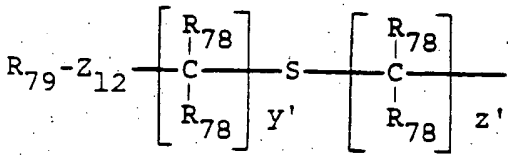
Alk denoted a linear or branched C_1-C_6 alkylene group,

a^5 represents 0 or the integer 1 or 2);



(wherein a^6 is 0 to 4 and

Ring A is 5-8C cycloalkenyl, bicycloheptyl, bicycloheptenyl or 4-7C saturated heterocyclyl containing 0, S, SO or SO_2);



(wherein Z_{12} is a 6-membered aromatic ring containing ≥ 1 N atom(s); where:

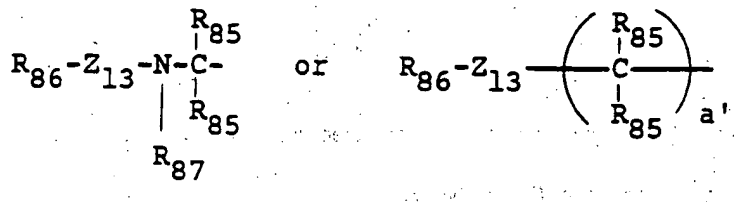
the ring is optionally substituted by (optionally substituted, optionally unsaturated) 1-6C alkyl, (optionally substituted) aryl, (optionally substituted) benzyl, OH, halogen, carbonyl, alkoxy, NO_2, $CONH_2$, (optionally substituted) NH_2 and/or carboxylate, such as pyridine, pyridazine, pyrimidine or pyrazine ring;

R_{78} is H or (optionally substituted, optionally unsubstituted) 1-4C alkyl;

R_{79} is H, (optionally substituted, optionally unsubstituted) 1-6C alkyl, (optionally substituted) aryl,

(optionally substituted) benzyl, OH, halogen, carbonyl, alkoxy, NO_2, $CONH_2$, (optionally substituted) amino or carboxylate,

y' + z' is 0 to 5);



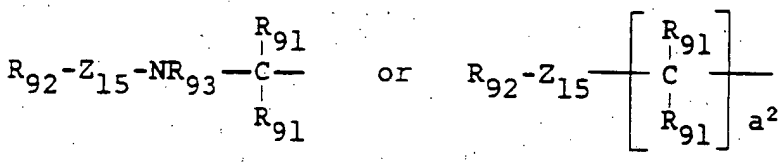
(wherein Z_{13} is a pyridine, pyridazine, pyrimidine or pyrazine ring, optionally substituted by optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, oxo, alkoxy, NO_2, amido, optionally substituted NH_2 or carboxylate;

R_{86} is H or optionally substituted, optionally unsaturated 1-4C alkyl;

R_{86} is one or more of H, optionally substituted, optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, oxo, alkoxy, NO_2, amido, optionally substituted NH_2 or carboxylate;

R_{87} is H, optionally substituted, optionally unsaturated 1-4C alkyl or acyl;

a' is 1-5);



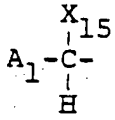
(wherein Z_{15} is a 6 membered aromatic ring containing one or more N atoms such as pyridine, pyridazine, pyrimidine or pyrazine, which ring may be substituted with one or more optionally substituted, optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, carbonyl, alkoxy, NO_2, amido, optionally substituted amino or carboxylate);

R_{91} is H or optionally substituted, optionally unsaturated 1-4C alkyl;

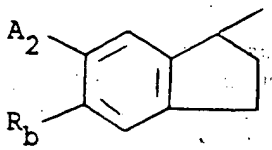
R_{92} is H or one or more substituents selected from optionally substituted, optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, carbonyl, alkoxy, NO_2, amido, optionally substituted amino or carboxylate;

R_{93} is H, optionally substituted, optionally unsaturated 1-4C alkyl or acyl;

a^2 is 1 to 5);



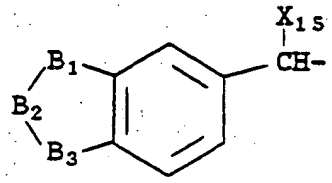
(wherein X_{15} is hydrogen, methyl, or ethyl, and A_1 is phenyl substituted in the para-position by isobutyl, cyclohexyl, alkoxy, or 1-pyrrolinyl and, optionally substituted additionally in the meta-position by fluorine or chlorine, or phenyl substituted in the meta-position by benzoyl or phenoxy, or phenyl substituted in the ortho-position by 2,4-dichlorophenoxy or 2,6-dichlorophenylamino);



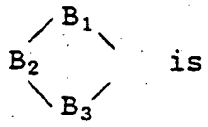
(wherein

R_6 is cyclohexyl or cyclophenylmethyl; and

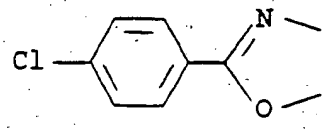
A_2 is hydrogen or chlorine);

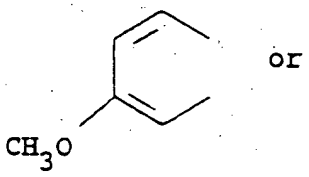


(wherein X_{15} is as defined above, and

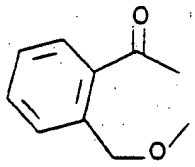


is

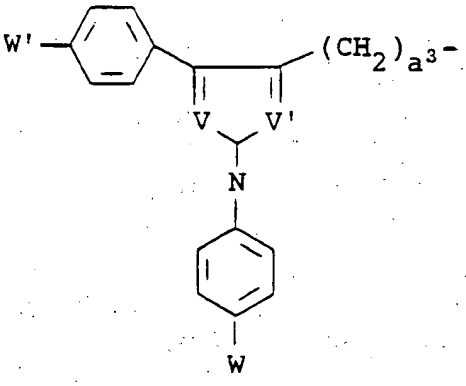




or



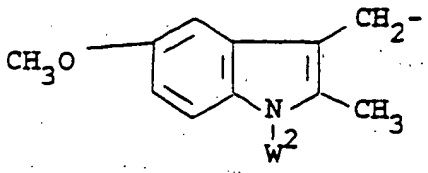
;



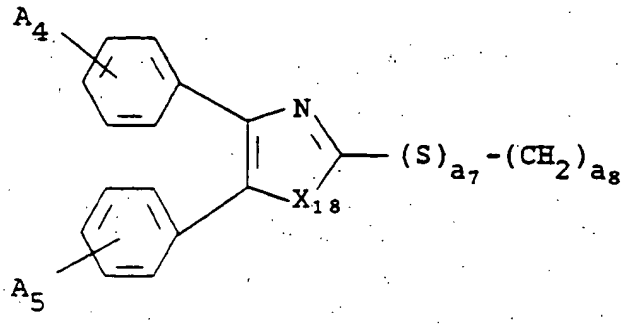
wherein a^3 is 1, 2 or 3;

W and W', are identical or different, and each is hydrogen, fluorine or chlorine, and

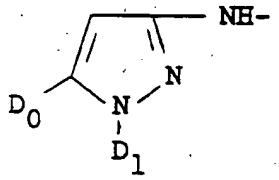
one of V and V' is nitrogen and the other is a methyne residue optionally substituted by a phenyl group, and



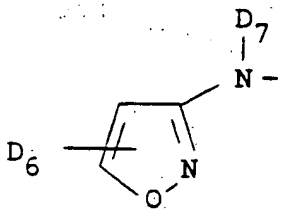
wherein W^2 is p-chlorobenzoyl or cinnamoyl);



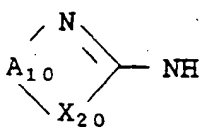
(wherein A_4 and A_5 are the same or different and are H, OH, lower alkoxy or halogen;
X_{15} is O, S or NH;
a_7 is 0 or 1;
a_8 is 0 or an integer of 1-6);



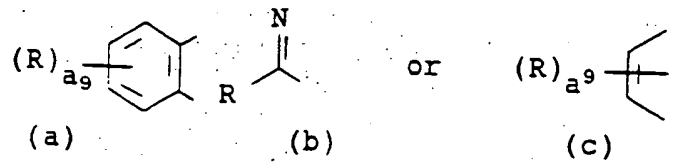
(wherein D_0 is H or alkyl;
D_1 is H or lower alkyl);



(wherein D_6 is H, 1-10C alkyl, 3-10C cycloalkyl, phenyl, 2-10C alkenyl (optionally substituted by phenyl) or phenyl(1-5C)alkyl (optionally ring-substituted by a 1-5C alkoxy);
D_7 is H or 2-6C alkanoyl);

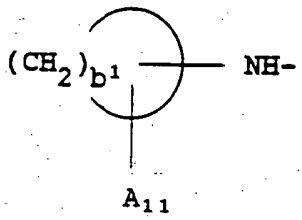


(wherein A_{10} is a group of formula (a)-(c):

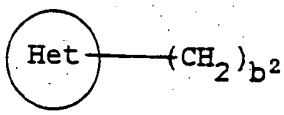


(a) (b) (c)

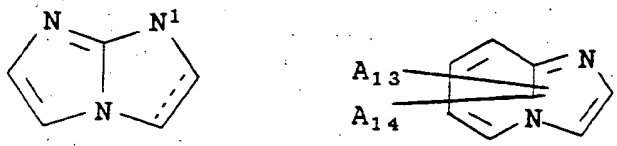
and X_{20} is O, S or NH);



(wherein A_{11} is H or 1-5C alkyl;
b_1 is 3-10);

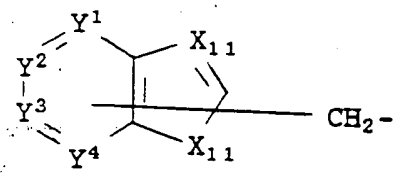


(wherein ring Het is a group of formula (A) or (B):



(A) (B)

the dotted line represents an optional double bond; A_{13}, A_{14} are H, 1-5C alkyl, halogen or OH);

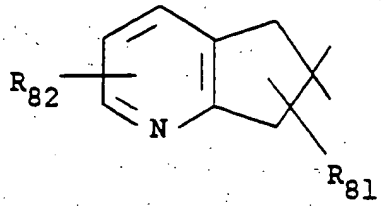


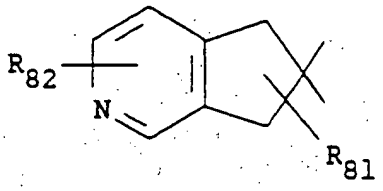
(wherein X_{11} are both N or one is N and the other is CH; one of Y^1-Y^4 is N and the rest is CH);

and the other of R^5 and R^6 is H, halogen, C_1-C_{30} alkyl, amino, alkylamino, dialkylamino, uriedo (NH_2CO-$N(R^{38})$- where R^{38} is H, alkyl, benzyl, phenyl optionally substituted with Cl or CH_3); alkenylamino, cycloalkylamino, aryloxy, pyridinium, guanidinium, ammonium, di-and tri-lower alkanolammonium, hydroxy, arylalkyl, alkoxy, alkylaryloxy, $-CH_2CO_2H$, $-CH_2PO_3H_2$, $-CH(PO_3H_2)(OH)$, $-CH_2CO_2C_2H_5$, $-CH_2CH(PO_3H_2)_2$,

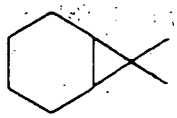
a hydrocarbyl radical as defined herein, a heterocyclic radical as defined herein, alkanoyl, an R^6 or R^5 radical as defined herein, a prodrug ester (such as (1-alkanoyloxy)alkyl, for example t-$C_4H_9CO_2CH_2$-, $CH_3CO_2CH_2$-);

at least one of R^5 and R^6 being a lipophilic group, or R^5 and R^6 can be joined to form a carbocyclic ring containing 3 to 12 carbons or a heterocyclic ring containing N, O and/or S atoms, such as of the formula





or

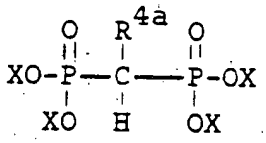


wherein R_{81} and R_{82} are each one or more substituents selected from H, optionally substituted saturated or unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, amido, OH, halogen, optionally substituted amino, amido, COOH, carbonyl, carboxylate, alkoxy and NO_2.

In another aspect of the present invention, a hypocholesterolemic or hypolipemic composition is provided formed of a bisphosphonate squalene synthetase inhibitor of structure I and a pharmaceutically acceptable carrier therefor.

The various preferred bisphosphonate compounds of structure I which may be employed in the method of the invention and/or hypocholesterolemic composition of the invention are outlined below.

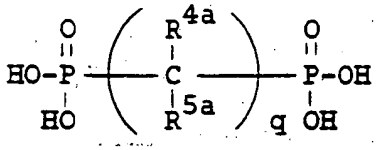
a) methylene diphosphonic acids and salts and esters as disclosed in U.S. Patent Nos. 3,299,123, 3,414,393 and 3,518,200 all to Fitch et al (all assigned to Monsanto), U.S. Patent Nos. 3,463,835, 3,471,406, 3,892,676 and 4,440,646 all to Budnick (all assigned to Plains Chemical Development Co.) (disclosed for use as surfactants, metal ion sequestering and deflocculating agents for detergents, gasoline additives, dry cleaning agents) having the formula



wherein R^{4a} is an aliphatic hydrocarbyl (for example, alkyl, aralkyl), alicyclic (for example, cycloalkyl), aryl, alkylaryl of from 5 to 30 carbon atoms and carbon containing heterocyclics (such as those set out above with respect to R^4 and R^5) (any of R^{4a} being optionally substituted with OH, halo, alkoxy, ester, ether, nitro, sulfonyl, amido, amino, carboxyl or nitroso); and

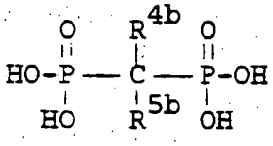
X is H, alkali metal, alkaline earth metal, aluminum, ammonium, amine and aliphatic hydrocarbyl, aryl, alkylaryl of from 1 to 30 carbons;

b) alkylenediphosphonic acids and/or salts disclosed in U.S. Patent Nos. 3,297,578 to Crutchfield et al, and 3,346,487 to Irani et al (both assigned to Monsanto) (used in detergents) and having the formula



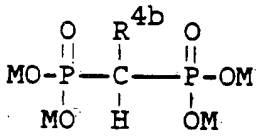
wherein R^{4a} is H or C_1-C_4 alkyl, and R^{5a} is H, OH or C_1-C_4 alkyl;

c) substituted methylene diphosphonic acids esters, or salts thereof as disclosed in U.S. Patent Nos. 3,404,178 and 3,422,021 each to Roy (both assigned to Procter & Gamble) (used in detergents) having the formula



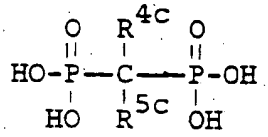
wherein R^{4b} and R^{5b} are each selected from H, methyl, benzyl or carboxymethylene (CH_2CO_2H), at least one of R^{4b} and R^{5b} being other than H;

d) alkyldiphosphonic acids, esters or salts as disclosed in U.S. Patent No. 3,609,075 to Barbera (assigned to Procter & Gamble) having the formula



wherein R^{4b} is alkyl of from 12 to 30 carbons and M is H, C_1 to C_8 alkyl, alkali metal or ammonium;

e) diphosphonates as disclosed in U.S. Patent Nos. 3,488,419 to McCune et al, 3,683,080 to Francis and 3,678,154 to Widder et al, (disclosed for use in compositions for inhibiting deposition and mobilization of calcium phosphate, arthritis, atherosclerosis) (not related to cholesterol biosynthesis inhibition or cholesterol lowering) having the formula



wherein R^{4c} is H, C_1 to C_{20} alkyl, C_2 to C_{20} alkenyl, aryl, phenylethenyl, benzyl, halo, amino, substituted amino (for example, dimethylamino, diethylamino, N-hydroxy-N-ethylamino, acetylamino), $-CH_2COOH$, $-CH_2PO_3H_2$, $-CH(PO_3H_2)(OH)$ or $-CH_2CH(PO_3H_2)_2$,

R^{5c} is H, lower alkyl, amino, benzyl, halo, OH, $-CH_2CO_2H$, $-CH_2PO_3H_2$, $-CH_2CH_2PO_3H_2$,

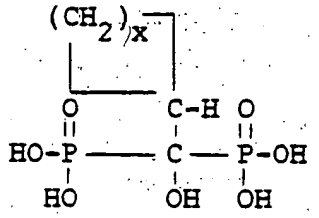
at least one of R^{4c} and R^{5c} being a lipophilic group;

[The following additional patents disclose type e) diphosphonate compounds:

U.S. Patent Nos. 4,330,530 to Baker (disclosed for use with gold salts for treating arthritis); 4,067,971 to Francis (disclosed for use in hypoxias and ischemic tissue diseases), 4,254,114 to Triebwasser (disclosed for use in control of pyrophosphate microorganisms), 4,137,309 to Van Duzee (disclosed for

use in sickle cell anemia), European Patent Application 88462A2 (disclosed for use with steroids for anti-inflammatory utilities)];

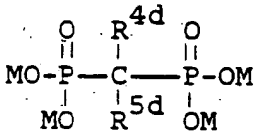
f) methanecycloalkylhydroxydiphosphinates as disclosed in U.S. Patent No. 3,553,314 to Francis (assigned to Procter & Gamble) [disclosed for use in oral compositions for calculus retardation and for treating deposition and mobilization of calcium phosphate including atherosclerosis (unrelated to cholesterol inhibition or lowering)] having the formula



wherein x is 1 to 7 so that the ring may contain 4 to 10 carbons, including salts thereof such as alkali-metal, alkaline earth metal, non-toxic heavy metal, ammonium or low molecular weight substituted ammonium.

[The following additional patents disclose type f) compounds: U.S. Patent Nos. 3,959,458 to Agricola et al, 4,025,616 and 3,934,002 both to Haefele (all relating to therapeutic substances for use in toothpaste compositions), and U.S. Patent No. 3,584,125 to Francis (relating to substances for inhibiting anomalous deposition and mobilization of calcium phosphates in animal tissue, arthritis, atherosclerosis (unrelated to cholesterol inhibition or lowering)); GB 1,453,667 (for containing radioactive P for treatment of tumors) (all assigned to Procter & Gamble)];

g) alkyldiphosphonates as disclosed in U.S. Patent No. 4,113,861 to Fleisch (assigned to Procter & Gamble) (disclosed or use in treatment of diabetes) having the formula



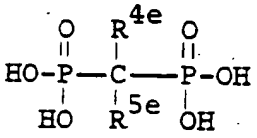
wherein R^{4d} is a C_2 or higher hydrocarbyl group (preferably containing 6 to 13 carbons) such as unsubstituted or substituted alkyl, cycloalkyl, alkenyl, alkynyl or carbocyclic group (cycloalkyl)

R^{5d} is H, OH or NH_2,

M is H, metal ion (such as alkali metal),

alkyl or aryl;

i) polyphosphonates as disclosed in U.S. Patent No. 4,761,406 to Flora et al (assigned to Procter & Gamble) (disclosed for treating or preventing osteoporosis) having the formula



wherein R^{4e} is R^7-X-$(CH_2)_a$-

wherein R^7 is H or a nitrogen-containing 6-membered aromatic ring (such as pyridyl, indanyl, hexahydroindanyl, picolyl);

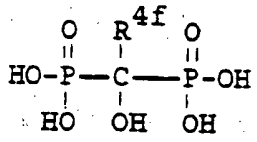
X is -NH-, oxygen or a single bond;

"a" is 0 to 7;

R^{5e} is H, Cl, amino or OH;

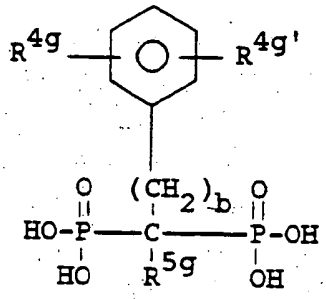
j) bisphosphonates as disclosed in Derwent No. 85-223756 (Akad Wissenschaft DDR) and DE 3804686

(Henkel) (disclosed for use in anticancer compositions) having the formula



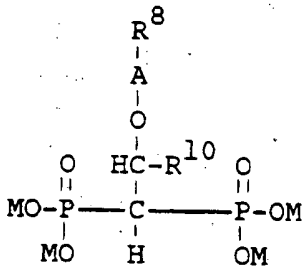
wherein R^{4f} is C_6 to C_{17} alkyl (Akad Wissenschaft) and C_1 to C_9 alkyl (Henkel) containing amino, carboxylate and other substituents);

k) bisphosphonates as disclosed in DE 3,425,746 (Amersham Buchler) (disclosed for use in diagnosis and treatment of bone tumors, and other diseases of the skeletal system) having the formula

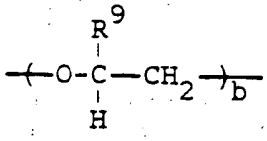


wherein R^{4g} and $R^{4g'}$ are independently H, alkyl, aryl, OH, alkoxy, aryloxy, amino, alkyl- or arylamino, carboxylalkyl, mercapto, alkyl- or arylthio, halo, nitro, cyano, sulfonic or sulfonamide, and R^{5g} is H, alkyl, aryl, OH, halo, amino, PO_3H_2 (alkyl has 1 to 6 carbons and is branched or unbranched, aryl has 6 to 14 carbons and either may be substituted);

l) oxa-alkane diphosphonic acids as disclosed in U.S. Patent No. 4,892,679 to Blum et al (assigned to Henkel Kommanditgeselsschaft) (disclosed for use as metal ion complexing agents and in diseases of calcium and phosphate metabolism) having the formula

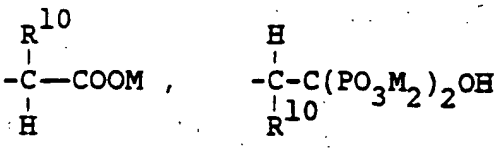


wherein A is



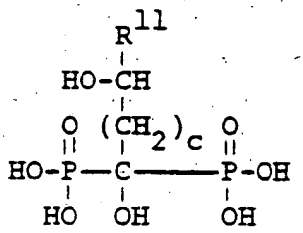
where b is 1 to 20,

R^8 is C_1-C_{10} alkyl, optionally substituted C_6-C_{10} aryl, phenylalkyl, naphthylalkyl,



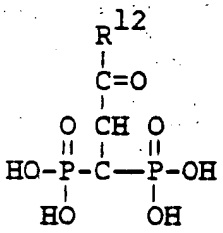
R^9 and R^{10} are independently H or CH_3; and
M is H or a monovalent cation;

m) dihydroxyalkane diphosphonic acids as disclosed in U.S. Patent No. 4,536,348 to Blum (assigned to Henkel) (disclosed for use as complexing and sequestering agents and in diseases of calcium and phosphate metabolism) having the formula



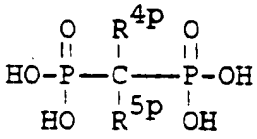
wherein R^{11} is H, phenyl, phenyl substituted with halo, C_1 to C_6 alkyl or OH and c is 1 to 9;

n) 3-oxo-propene-1,1-diphosphonic acids as disclosed in European Patent 0301352A2 (disclosed for use as a calcium complexing agent and in diseases of calcium and phosphate metabolism and tartar prevention) having the formula



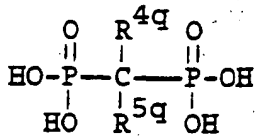
wherein R^{12} is tert-alkyl CR^{13}, R^{14}, R^{15} (wherein R^{13} and R^{14} are independently C_1-C_3 alkyl and R^{15} is C_1-C_{10} alkyl); cycloalkyl; aryl; or heteroaryl; or cycloalkyl, aryl or heteroaryl substituted with halo, C_1-C_4 alkyl, alkoxy or dialkylamino;

o) lipophilic bisphosphonates as disclosed in WO88/00829 (Leo Pharmaceutical Products) (disclosed for use for nasal administration in diseases involving calcium metabolism and arthritis) having the formula



wherein R^{4p} is alkyl, phenoxy, 4-Cl-C_6H_4-S-CH_2- and R^{5p} is H or OH;

p) methylene bisphosphonic acids as disclosed in WO86/00902 (Leo Pharmaceutical Products) (disclosed for use in various diseases involving calcium phosphate deposition or resorption, including atherosclerosis, and prevention of dental calculus) having the formula



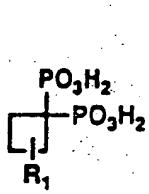
wherein R^{4q} is R^{15}-$(QCH_2CH_2)_dO$- wherein R^{15} is a straight or branched, saturated or unsaturated aliphatic or alicyclic C_1-C_{10} hydrocarbon radical, an aryl or an aryl-C_1-C_4-alkyl radical, R_1 if desired being unsubstituted or substituted with straight or branched C_1-C_4-alkyl, amino, C_1-C_4-alkylamino, di-(C_1-C_4-alkyl)-amino, carboxy, C_1-C_4-alkoxycarbonyl, hydroxy, C_1-C_4-alkoxy, phenoxy, mercapto, C_1-C_4-alkylthio, phenylthio, halogen, trifluoromethyl;

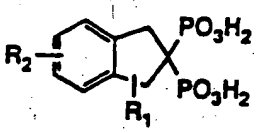
R^{5q} is hydrogen, C_1-C_8-alkyl, aryl-C_1-C_4-alkyl or halogen;

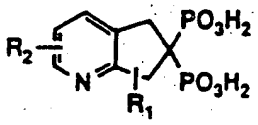
Q is O or S, and d is 0, 1 or 2; with the proviso that R^{5q} cannot be hydrogen or methyl if d = O and R^{1b} is methyl,

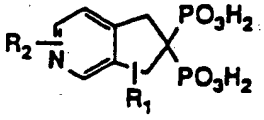
including double esters thereof;

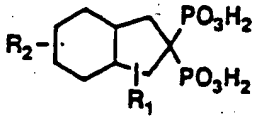
q) cyclic diphosphonic acids as disclosed in U.S. Patent No. 4,687,768 and European Patent Applications 0304961 and 0304962 all to Benedict et al and assigned to Procter & Gamble (disclosed for treating diseases characterized by abnormal calcium and phosphate metabolism) having the formula

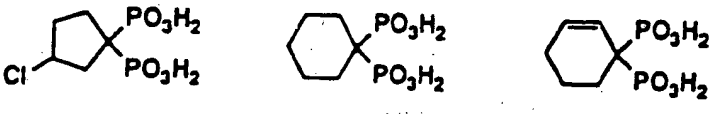


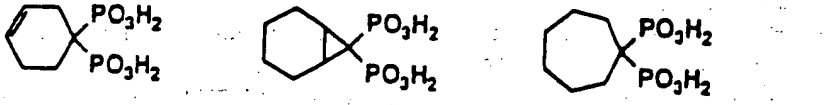










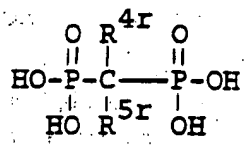


wherein R_1 represents one or more substituents including alkyl, alkenyl, aryl, benzyl, hydroxy, halogen, amino, amido, carboxy, carbonyl, carboxylate, alkoxy and combinations thereof, and

R_2 represents hydrogen, nitro, or any of the groups defined under R_1;

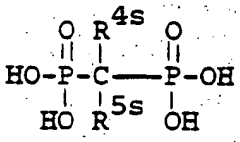
wherein the above R_1 and/or R_2 groups may optionally include substituents such as alkyl, alkenyl, aryl, halogen, hydroxy or cycloalkyl;

r) bisphosphonates as disclosed in U.S. Patent No. 4,515,766 to Castronovo et al (assigned to Mass. Gen. Hosp.) (disclosed for use in forming radiolabeled compounds for scanning for calcium deposits) having the formula



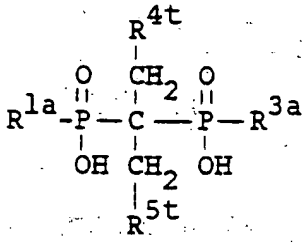
wherein R^{4r} is aryl, and R^{5r} is H, alkyl, alkenyl, amino, benzyl, OH, $-CH_2PO_3H$, $-CH_2CH_2PO_3O_2$.

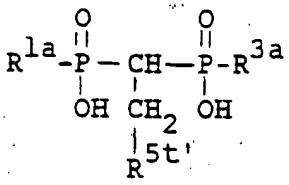
s) bisphosphonates as disclosed in Derwent No. 79-00757C/01 (Japanese Patent No. 55-4147-925) (disclosed for use as herbicides) having the formula



wherein R^{4s} and R^{5s} are independently H, halo, alkyl or cycloalkyl, at least one of R^{4s} and R^{5s} being a lipophilic group;

t) diphosphonic acids as disclosed in U.S. Patent Nos. 4,836,956 and 4,818,774 each to Kem (each assigned to Occidental Chemical Corp) (disclosed for use in extraction of uranium and other metals from water) having the formula





wherein R^{1a} and R^{3a} are the same or different and are alkyl and alkylaryl groups having from 1 to about 18 carbon atoms or hydroxyl;

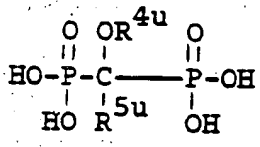
R^{4t} is independently selected from substituted or unsubstituted alkyl or alkylaryl groups having 1 to about 18 carbon atoms or hydrogen;

R^{5t} is independently selected from alkyl or alkylaryl groups having 1 to about 18 carbon atoms; provided that the sum of carbon atoms of the R groups is at least 15; and

$R^{5t'}$ is independently selected from substituted and unsubstituted alkyl or alkylaryl groups having 1 to about 18 carbon atoms or a polymeric group; provided that the sum of the carbon atoms of the R^1, R^{1a}, R^{3a} and $R^{5t'}$ groups is a least 16.

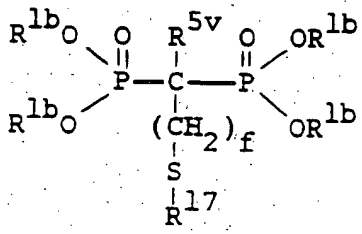
Substituted alkyl and alkylaryl groups include alkyl and alkylaryl groups substituted with moieties, such as fluoro, chloro, bromo, iodo and hydroxyl groups;

u) bisphosphonate acids as disclosed in European Patent Application 185589A (Rhone-Poulenc) (used for treatment of Paget's disease and osteoporosis) having the formula



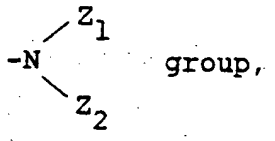
wherein R^{4u} is C_2 or C_3 alkyl and R^{5u} is H or alkyl; or R^{4u} is C_{1-3} alkyl and R^{5u} is C_{1-2} alkyl.

v) methylene diphosphonic acids as disclosed in U.S. Patent Nos. 4,746,654 and 4,876,248 both to Breliere (both assigned to Sanofi) (disclosed for use as anti-inflammatory agents) having the formula

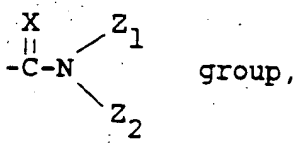


wherein R^{1b} is hydrogen or a straight or branched lower alkyl group having from 1 to 4 carbon atoms;

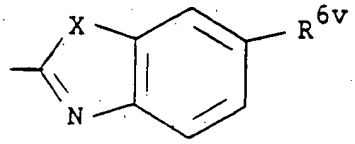
R^{17} is hydrogen, an alkyl group which is unsubstituted or substituted by a hydroxyl group, a thiol group, one or more halogen atoms, an alkoxycarbonyl group or a



where Z_1 and Z_2, considered independently of one another, are hydrogen or a lower alkyl group, a phenyl group which is unsubstituted or has one or more halogen, nitro group, lower alkyl group, lower alkoxy group, trifluoromethyl, NH_2 group, COOH group or COOalkyl group, a

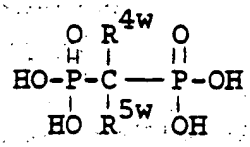


where X is oxygen or sulfur and Z_1 and Z_2 are as defined above, a heterocyclic radical with 5 or 6 members, containing 1 or 2 heteroatoms chosen from amongst nitrogen and sulfur, or, a heterocyclic radical with 5 members fused to a benzene ring and having the formula



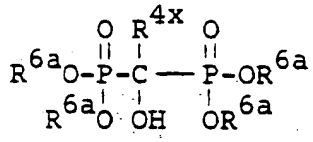
where X is oxygen, an NH group or sulfur and R^{6v} is hydrogen or a halogen atom, preferably chlorine, R^{5v} is hydrogen or a hydroxyl group, and f is an integer between 0 and 10, with the proviso that f cannot be 0 if R^{5v} is OH;

w) bisphosphonic acids as disclosed in European Patent Application 336851A (Sanofi) (disclosed for use with sodium lauryl sulfate (for oral availability) for treating rheumatism and arthritis) having the formula



wherein R^{4w} is halo, C_{1-5} alkyl (optionally substituted with Cl, OH, NH_2 or dialkylamino), phenoxy, phenyl, thio, phenylthio, chlorophenylthio, pyridyl, 4-thiomorpholinyl and R^{5W} is H, halo, OH, NH_2, dialkylamino;

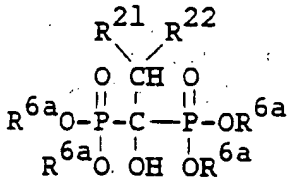
x) diphosphonic acids as disclosed in U.S. Patent No. 4,503,049 to Biere et al (assigned to Schering A.G.) (disclosed for use as anti-inflammatory and antiarthritic agents and for diseases involving calcium) having the structure



wherein R^{6a} is hydrogen, an alkali metal atom, an alkaline earth metal atom, or alkyl of 1-4 carbon atoms, and R^{4x} is the residue of a carboxylic acid containing an aromatic or heteroaromatic group and being of the formula

arylCOOH,

diphosphonic acid derivatives of the formula

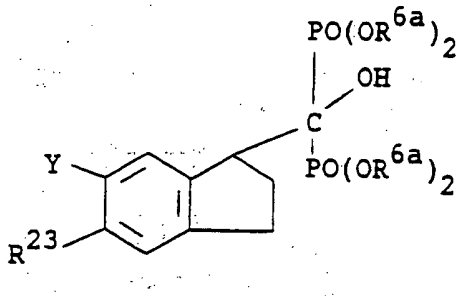


wherein R^{6a} is as defined above;

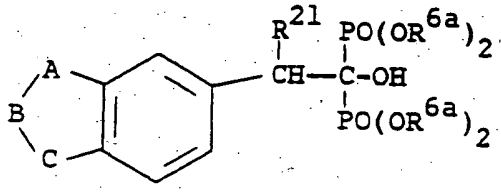
R^{21} is hydrogen, methyl, or ethyl; and

R^{22} is phenyl substituted in the para-position by isobutyl, cyclohexyl, alkoxy, or 1-pyrrolinyl and, optionally substituted additionally in the meta-position by fluorine or chlorine; or phenyl substituted in the meta-position by benzoyl or phenoxy, or phenyl substituted in the ortho-position by 2,4-dichlorophenoxy or 2,6-dichlorophenylamino;

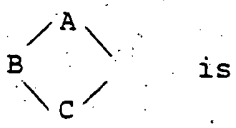
diphosphonic acid derivatives of the formula



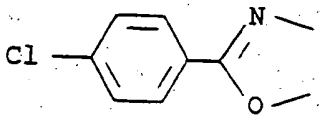
wherein R^{6a} is as defined above;
R^{23} is cyclohexyl or cyclopentylmethyl; and Y is hydrogen or chlorine;
diphosphonic acid derivatives of the formula

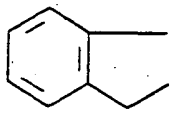


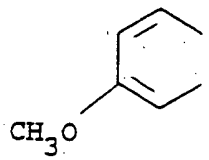
wherein R^{6a} and R^{21} are as defined above, and



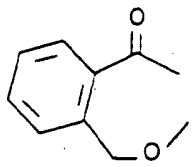
is





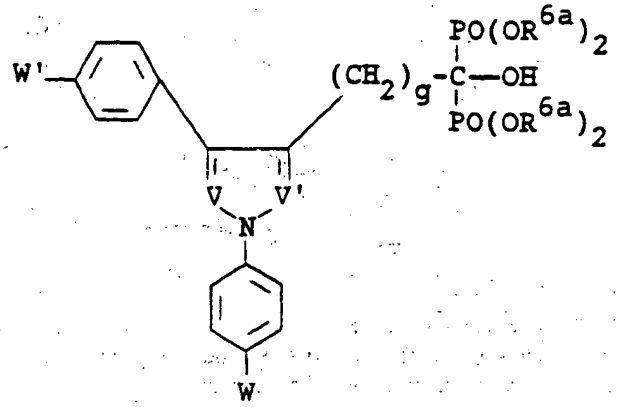


or



;

diphosphonic acid derivatives of the formula



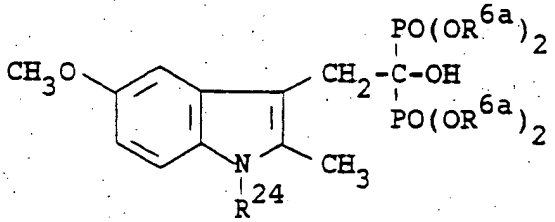
wherein g is 1, 2, or 3;

R^{6a} is as defined above;

W and W', are identical or different, and each is hydrogen, fluorine or chlorine, and

one of V and V' is nitrogen and the other is a methyne residue optionally substituted by a phenyl group; and

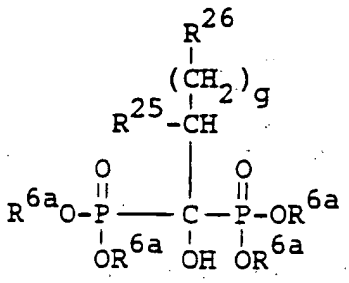
diphosphonic acid derivatives of the formula



wherein R^{6a} is as defined above, and

R^{24} is p-chlorobenzoyl or cinnamoyl; or, throughout, when R^{6a} is H, a physiologically acceptable salt thereof with an organic base;

y) diphosphonic acids as disclosed in U.S. Patent No. 4,473,560 to Biere et al (assigned to Schering AG) (disclosed for use as anti-inflammatory and antiarthritic agents, and for diseases involving calcium, such as Paget's disease, osteoporosis, and ectopic calcification) having the formula



wherein g is 0, 1 or 2;

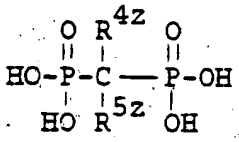
R^{25} is H or C_1-C_4 alkyl;

R^{6a} is H, alkali metal, alkaline earth metal, or C_1-C_4 alkyl; and

R^{26} is phenyl optionally substituted by F atom(s), Cl atom(s), alkyl group(s) of 1-4 carbons, alkoxy group(s) of 1-4 carbons; naphthyl; biphenyl; or thienyl; or salts thereof;

z) bisphosphonates as disclosed in Japanese Patent JK 73-54,278 (used in peroxide bleaching solutions)

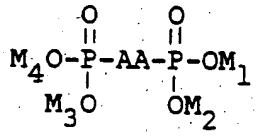
having the formula



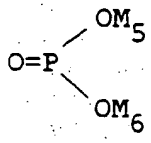
wherein R^{4z} is H or alkyl and

R^{5z} is H, OH or alkyl, at least one of R^{4z} and R^{5z} being a lipophilic group;

aa) alkylenepolyphosphonic acids as disclosed in U.S. Patent No. 4,276,089 to Moran (assigned to Union Chimique et Industrielle de l'Ouest S.A.) (disclosed for use with polyamines as corrosion inhibitors) having the structure

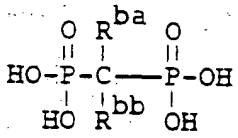


wherein AA represents a bivalent alkylene group which is a straight and saturated C_1-C_{10} hydrocarbon chain, each carbon of which may be optionally substituted by at least one of OH, C_1-C_4 alkyl and phosphonic group



and M_1 to M_6 may be the same or different and are H, C_1-C_4 alkyl, NH_4^+ or a metal cation;

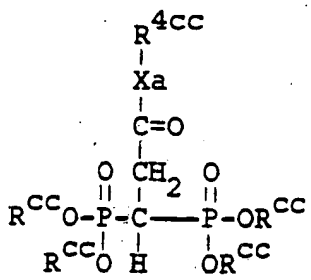
bb) bisphosphonates as disclosed in DD 237,252A, Derwent No. 86-291914/45 (assigned to Veb Chem Bitterfeld) (disclosed for use as a plant growth regulator) having the formula



wherein R^{ba} is H, lower alkyl, pyrrolidino or piperidino and

R^{bb} is H, OH or lower alkyl, at least one of R^{ba} and R^{bb} being a lipophilic group;

cc) bisphosphonates as disclosed in Japanese Patent No. J-6-3,295,595A, Derwent No. 89-019688/03 (assigned to Yamanouchi Pharm KK) (disclosed or use as anti-inflammatory, and analgesic agents, and for bone abnormalities due to rheumatism, arthritis and osteoporosis), having the formula

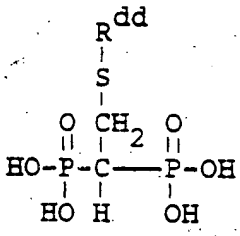


wherein R^{cc} is H or lower alkyl;

Xa is NH or a bond; and

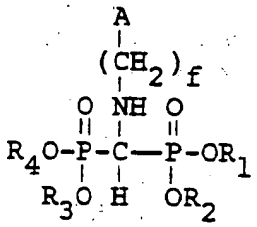
R^{4cc} is phenyl or pyrrolyl each optionally substituted with alkyl;

dd) bisphosphonates as disclosed in USSR SU 862,439 (disclosed for use as collecting agents for the flotation of tin containing ore) having the formula



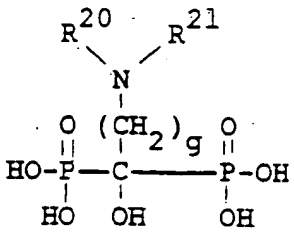
wherein R^{dd} is a C_3-C_{10} aliphatic (such as alkyl), aromatic (such as phenyl) or arylaliphatic (such as benzyl) hydrocarbyl group;

ee) substituted aminomethylenebis(phosphonic acid) derivatives as disclosed in European Patent Application 337706 (Yamanouchi Pharmaceutical Co.) (disclosed for use in bone resorption-inhibitory and anti-inflammatory effects) having the formula



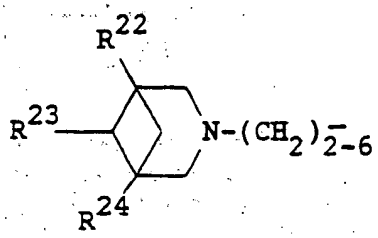
wherein R_1-R_4 is H or alkyl, f is o to 4 and A is C_5-C_8 cycloalkenyl, bicycloheptyl, bicycloheptenyl, saturated C_4-C_7 heterocyclyl containing O, S, SO or SO_2;

ff) araliphatyl aminoalkyldiphosphonic acids as disclosed in European Patent Application 320455 (Ciba-Geigy) (disclosed for use in disorders of calcium metabolism) having the formula



wherein R^{20} is arylaliphatic residue, R^{21} is H or aliphatic residue, and $(CH_2)_g$ is a divalent aliphatic residue where g is 1 to 6;

gg) azabicycloheptanes as disclosed in European Patent Application 317506 (Ciba-Geigy) (disclosed for use as calcium metabolism modulators) having the formula I wherein R^5 is

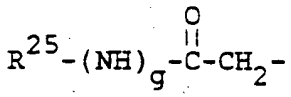


(wherein R^{22} is H, C_1-C_{20}alkyl, alkoxy, aryl;

R^{23} is H, C_1-C_{20}alkyl, alkoxy, aryl, halo, carboxyl;

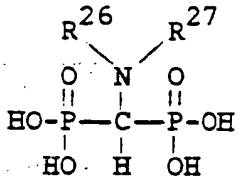
R^{24} is H, C_1-C_{20}alkyl, alkoxy);

hh) 3-oxopropylidene-1,1-diphosphonates as disclosed in Japanese Patent Application 87-271,433 (Yamanouchi Pharmaceutical Co.) (disclosed for use as inflammation inhibitors, analgesics, antipyretics) having the formula I wherein R^5 is



wherein R^{25} is (alkyl-substituted)pyrrolyl or phenyl and g is 0 or 1;

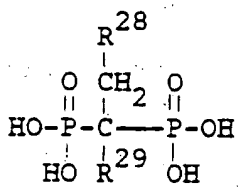
ii) (aminomethylene)diphosphonic acids as disclosed in Japanese Patent 63150290 (Ciba-Geigy) having the structure



wherein R^{26} is (benzo- or cyclohexeno-fused) 5-membered heteroaryl containing 2 to 4 N atoms or 1-2 N atoms plus an O or S atom with optional substituents such as alkyl or halo;

R^{27} is K or alkyl, but R^{27} is alkyl when R^{26} is (alkyl and/or halo-substituted) pyrazol-3-yl or isoxazol-3-yl;

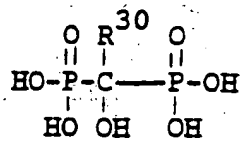
jj) alkylenediphosphonic acids as disclosed in Japanese Patent 63150291 (Ciba-Geigy) having the formula



wherein R^{28} is a 5-membered heteroaryl containing 2-4 N atoms or 1-2 N atoms plus an O or S atom optionally substituted with alkyl or halo, and

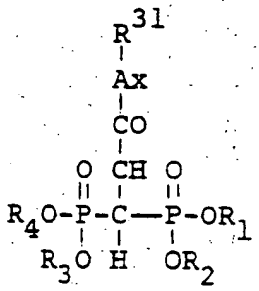
R^{29} is H, OH, NH_2, alkylthio or halo;

kk) azacycloalkylalkanediphosphonic acids as disclosed in EP 272208 (Ciba-Geigy) (disclosed for use as regulators of calcium metabolism) having the formula



wherein R^{30} is aromatic-substituted mono- or biazacyclylalkyl (alkyl bonds with N in heterocycle);

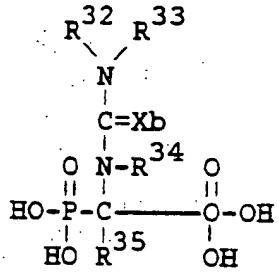
ll) 2-substituted-2-oxoethylene-1,1-diphosphonic acids as disclosed in Japanese Patent 63185993 (Yamanouchi Pharmaceutical Co.) (disclosed for use in bone disorders, anti-inflammatories) having the structure



wherein R_1-R_4 is H or lower alkyl, Ax is phenyl, naphthyl, mono- or bicyclic N-containing heterocycles, and

R^{31} is H, halo, lower alkoxy, lower alkyl;

mm) ureidoalkylbisphosphonic acids as disclosed in Japanese Patent 63088192 (Fujisawa Pharmaceutical Co.) (disclosed for use as bone absorption inhibitors) having the formula



wherein R^{32} is optionally substituted aryl, optionally substituted aralkyl, or optionally substituted alkyl,

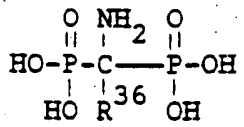
R^{33} is H or aryl,

R^{34} and R^{35} are H or alkyl, and

Xb is O or S;

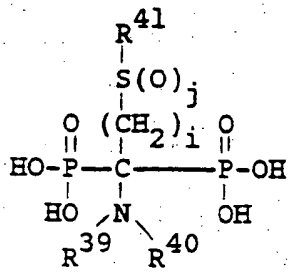
nn) heterocyclicalkyl diphosphonic acids as disclosed in DE 3640938 (Boehringer Mannheim) (for use in treating calcium metabolic disorders) such as 1-(decahydroquinolin-3-yl)methane-1-hydroxy-1,1-diphosphonic acid, di Na salt;

oo) 1-aminoalkyl-1,1-bisphosphonic acids as disclosed in DD 222598 (Akademie der Wissenschaften) having the formula



wherein R^{36} is C_2-C_{12} alkyl.

pp) methylenediphosphonic acids as disclosed in EP 151072 (Sanofi) (disclosed for use in anti-inflammatory and antiarthritic compositions) having the formula

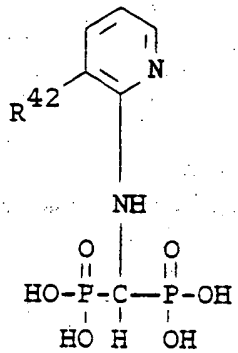


wherein R^{39} is H, alkyl or $CONH_2$,

R^{40} is H, alkyl, benzyl, optionally substituted phenyl (such as with Cl or CH_3), or R^{39}, R^{40} are $(CH_2)_{4,5}$, j is 0, 1 or 2, i is 1 to 5,

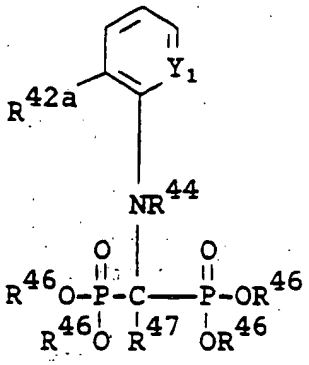
R^{41} is alkyl, cycloalkyl, optionally substituted phenyl or heterocyclyl;

qq) N-(unsubstituted or substituted pyridyl)amino-methylene diphosphonic acids as disclosed in U.S. Patent No. 4,447,256 (Nissan Chemical Industries) (disclosed for use as herbicides) having the formula



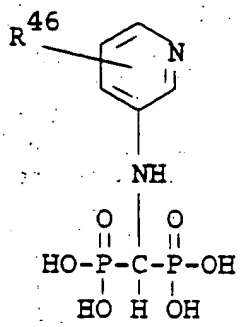
wherein R^{42} is H, alkyl or halo;

rr) pyridylaminomethylenediphosphonates as disclosed in Japanese Patent 55089210 (Nissan Chemical Industries) (disclosed for use as herbicides) having the formula



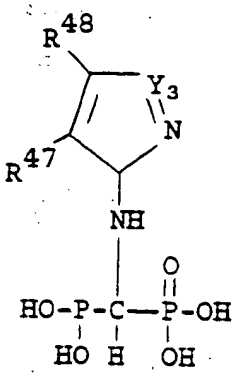
wherein R^{46} is OH, halo, phenoxy or alkylamino,
R^{47} is H or halo,
R^{44} is H or aliphatic acyl (such as alkanoyl or alkenoyl),
R^{42a} is alkyl, and
Y_1 is N, NO or $NR^{43}Y_2$, wherein R^{43} is alkyl and Y_2 is halo;

ss) pyridylbisphosphonates as disclosed in Japanese Patent 55098105 (Nissan Chemical Industries) (disclosed for use as herbicides) having the formula



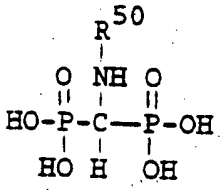
wherein R^{46} is H, halo or alkyl;

tt) bisphosphonates as disclosed in Japanese Patent 55089293 (Nissan Chemical Industries) (disclosed for use as herbicides) having the formula

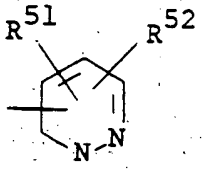


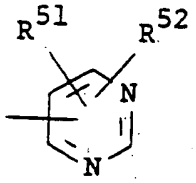
wherein Y_3 is O or NH, R^4 is H, alkyl or halo, and R^{48} is H or alkyl;

uu) diphosphonic acids as disclosed in Japanese Patent 54144383 (Nissan Chemical Industries) (disclosed for use as herbicides) having the formula

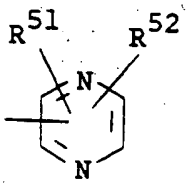


wherein R^{50} is



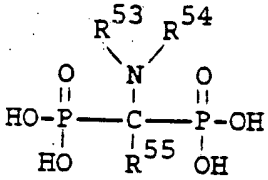


or



wherein R^{51} and R^{52} are H, halo, alkyl or hydroxy;

vv) diphosphonates as disclosed in Japanese Patent 54037829 (Nissan Chemical Industries) (disclosed for use as herbicides) having the formula

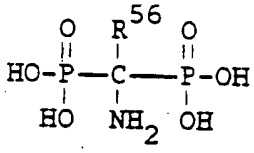


wherein R^{53} is H, alkyl, alkenyl, benzyl or ethylcarbonyloxymethyl,

R^{54} is H, alkyl, alkenyl or cyclohexyl,

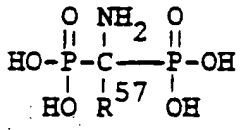
R^{55} is H, alkyl, alkenyl or ethylcarbonyloxymethyl;

ww) disphosphonates as disclosed in UK 1508772 and DE 2625767 (Benckiser-Knapsack) (Shell) having the formula



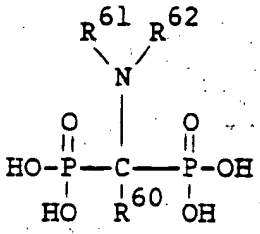
wherein R^{56} is C_5-C_{12} alkyl, aryl or aralkyl;

xx) 1-aminoalkylidene-1,1-diphosphonic acids as disclosed in DE 2115737 (Henkel) (disclosed for use as water softeners) having the formula



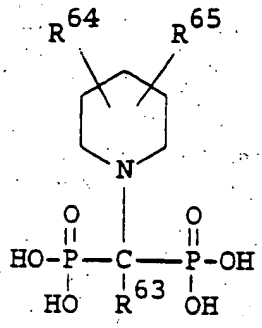
wherein R^{57} is CH_3, propyl, n-heptyl, n-$C_{11}H_{23}$, n-$C_{15}H_{31}$, i-propyl;

yy) 1-amino-alkylidenediphosphonic acids as disclosed in DE 2048912 and DE 2048913 (Henkel) (disclosed for use as water softeners) having the formula



wherein R^{60} is H, CH_3, n-nonyl, phenyl, benzyl or CH_2CO_2H, R^{61} and R^{62} are H or CH_3;

zz) 1-piperidinoalkane-1,1-diphosphonic acids as disclosed in Japanese Patent 53059674 (Nissan chemical Industries) (disclosed for use as herbicides) having the formula

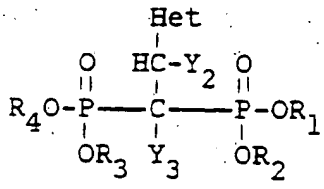


wherein R^{63} is H or CH_3,

R^{64} is alkyl, and

R^{65} is H or alkyl;

aaa) heterocyclically substituted alkane-1,1-diphosphonic acids as disclosed in EP 170228A (Boehringer Mannheim) (disclosed for use as anti-inflammatory agents) having the structure



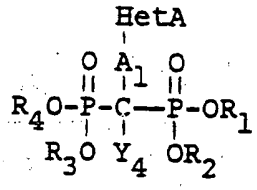
wherein Het is a heteroaromatic 5-membered ring with 2 or 3 heteroatoms, optionally partially hydrogenated and optionally substituted by one or more alkyl, alkoxy, phenyl, cyclohexyl, cyclohexylmethyl, halo or amino, with 2 adjacent alkyl optionally together forming a ring (Het cannot be pyrazole),

Y_2 is H or lower alkyl, and

Y_3 is H, OH, amino or alkylamino;

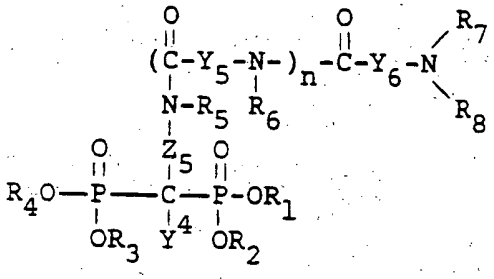
bbb) diphosphonic acids as disclosed in U.S. Patent No. 4,687,767 (Boehringer Mannheim) (disclosed for

use in calcium metabolism disturbances) having the formula



wherein HetA is imidazole, oxazole, isoxazole, thiazole, pyridine, 1,2,3-triazole, 1,2,4-triazole or benzimidazole, the above heterocyclics optionally substituted by alkyl, alkoxy, halo, OH, carboxyl, amino optionally substituted by alkyl or alkanoyl or a benzyl optionally substituted by alkyl, nitro, amino or aminoalkyl, A_1 is a straight-chained or branched saturated or unsaturated hydrocarbon chain containing 2 to 8 carbons, Y_3 is H, OH, alkanoyl;

bbb') diphosphonic acids as disclosed in U.S. Patent No. 4,666,895 (Boehringer Mannheim) (disclosed for use in calcium metabolism disturbances) having the formula



wherein Y_4 is H or OH,

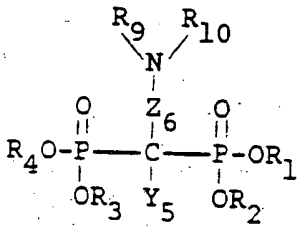
R_1-R_8 are independently H or lower alkyl, whereby R_7 and Y_6, or R_6 and Y_5, or R_5 and Z_5, together with the nitrogen atoms to which they are attached can form a 5- or 6-membered ring,

Y_6 and Y_5 which can be the same or different are C_1-C_6 alkylene chains optionally substituted by aromatic or heteroaromatic radicals,

Z_5 is C_1 to C_6 alkylene which can include heteroatoms and optionally substituted by aromatic or heteroaromatic,

n is 0, 1 or 2;

ccc) omega amino-alkane-1,1-diphosphonic acids as disclosed in DE 623397 (Boehringer Mannheim) (disclosed for use in disorders of calcium metabolism) having the formula



wherein R_1-R_4 are H or C_1-C_4 alkyl,

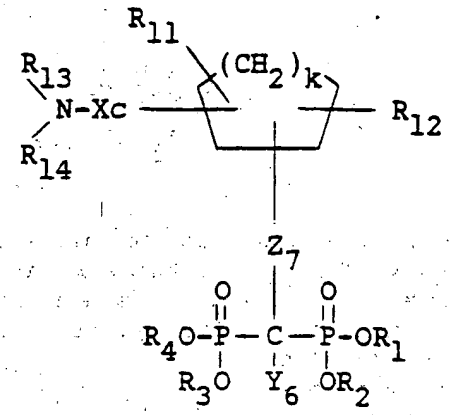
Z_6 is C_1-C_6 alkylene,

R_9 is saturated or unsaturated C_4-C_9 alkyl optionally substituted by phenyl or cyclohexyl,

R_{10} is cyclohexyl, cyclohexylmethyl, benzyl or saturated or unsaturated C_4-C_{18} alkyl optionally substituted by phenyl or optionally esterified or etherified OH, and

Y_5 is H, OH, or mono- or di(C_1-C_6 alkyl)amino;

ddd) aminocycloalkane diphosphonates as disclosed in DE 3,540,150 (Boehringer Mannheim) (disclosed for use in calcium metabolic disorders) having the structure



wherein R_1-R_4 are H or alkyl,

Xc is a bond or alkylene,

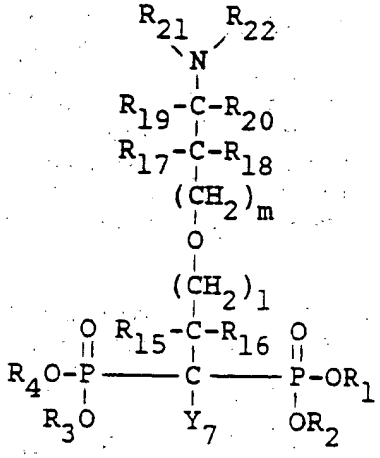
R_{13}, R_{14} are H, acyl, alkyl or aralkyl, R_{11}, R_{12} are H, alkyl or

R_{11}, R_{12} are together $(CH_2)_k$,

Z_7 is a bond or (amino)alkylene,

Y_6 is H, OH, amino and k is 1 to 3;

eee) amino-oxa-alkane-diphosphonic acids as disclosed in DE 822650 (Boehringer Mannheim) (disclosed for use in calcium metabolism disorders) having the structure



R_{21} and R_{22} are independently H, saturated or unsaturated 1-9C alkyl (optionally substituted by OH, 1-5C alkoxy, 1-5C alkylthio, Aryl or 5-7C cycloalkyl) 5-7C cycloalkyl or phenyl;

Aryl is phenyl optionally substituted by 1-5C alkyl, 1-5C alkoxy, OH or halogen;

R_{19} is H, 1-5C alkyl (optionally substituted by OH, 1-5C alkoxy, 1-5C alkylthio, SH, phenyl, 3-indolyl or 4-imidazolyl), or phenyl optionally substituted by OH or 1-5C alkoxy;

R_1-R_4, R_{20}, R_{18}, R_{16} are independently H or 1-5C alkyl;

R_{15} and R_{17} are independently H, 1-5C alkyl, or phenyl optionally substituted by OH or 1-5C alkoxy;

Y_7 is H, OH or $NR_{23}R_{24}$;

R_{23} and R_{24} are independently H or 1-5C alkyl;

m and l are independently 0 or 1;

or NR_{21} R_{22} is a 4-9C mono- or bicyclic ring system which is partially or totally hydrogenated and is optionally substituted by OH, 1-5C alkyl or 1-5C alkoxy, where monocyclic rings may also contain an O,

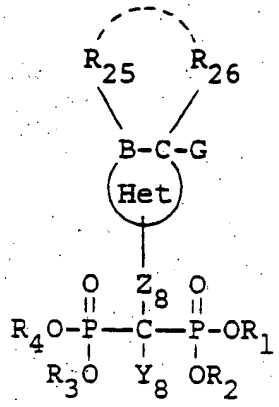
N or S atom;

or R_{21} + R_{20} forms a 5- or 6-membered ring, optionally fused with another 6-membered ring;

or R_{21} + R_{18} forms a 5- or 6-membered ring;

or R_{20} + R_{19}, R_{19} + R_{18}, R_{18} + R_{17} and/or R_{15} + R_{16} forms a 5- or 6-membered ring.

fff) diphosphonic acids as disclosed in DE 640938 (Boehringer Mannheim) (disclosed for use in calcium metabolism disorders) having the structure



wherein Het is a hydrogenated or partially hydrogenated heterocycle containing 1 or 2 N atoms, each optionally substituted with alkyl, benzyl or cyclohexylmethyl;

B is N or CH and the bond connnecting B to the C atom to which G is attached can be a single or a double bond;

R_{25} and R_{26} are independently H or lower alkyl, or together form a 3-5C alkylene chain, and this ring fused with Het may contain up to 3 double bonds;

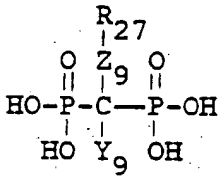
R_1 to R_4 are H or lower alkyl;

Z_8 is a single bond or optionally branched 1-6C alkylene which may not be attached to a heteroatom;

Y_8 is H, OH or amino;

G is H; and provided that, if Y_8 is a single bond, Het is not a pyrrolidine ring which is 2-substituted by Y_8;

ggg) methylenediphosphonic acids as disclosed in EP 243173A (Fujisawa Pharm KK) (disclosed for use in abnormal bone metabolism) having the formula



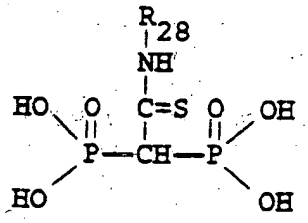
wherein R_{27} is aryl or heterocyclyl both optionally substituted by one or more of lower alkyl, lower alkoxy, lower alkylthio, halo(lower)alkyl, acyl, acylamino or halo or R_{27} is lower alkyl substituted by heterocyclyl which is optionally substituted by acyl;

R_{27}-Z_9- is R_{27}-NHC(=X_9)-; R_{27}-C(=O)NH-; or R_{27}-SO_2-NH-;

X_9 is O or S;

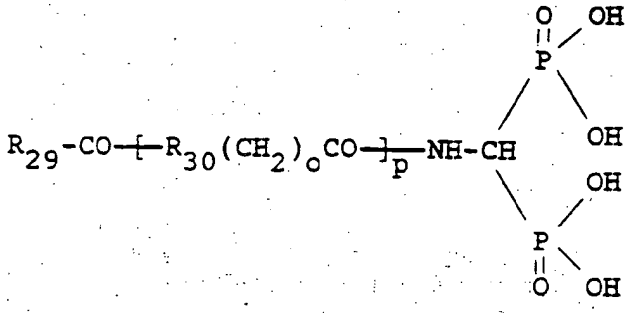
Y_9 is H or lower alkyl, provided that when R_{27} is lower alkyl then R_{27}-Z_9- is R_{27}NHC(X)- or $R_{27}SO_2NH$-;

hhh) diphosphonic acids as disclosed in Japanese Patent 261275 (Fujisawa Pharm) (disclosed for use in bone disorders) having the formula



wherein R_{28} is phenyl, pyridyl or quinoiyl substituted by lower alkylsulphonylamino halo-lower alkylsulphonylamino and mono- or di-lower alkylamino;

hhh) diphosphonic acids as disclosed in Japanese Patent 259896 (Fujisawa Pharm) (disclosed for use as anti-inflammatory agents) having the formula



wherein R_{29}-CO- is a residue of pharmaceutically active compound R_{29}-COOH;

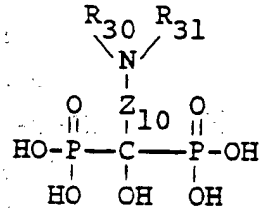
R_{30} = -NH- or -O-;

p = 0 or 1;

o = 1-10;

R_{29}-COOH is an anti-inflammatory agent, e.g. diclofenac, ibuprofen, mefenamic acid, aspirin, naproxen, ketoprofen, indomethacin or sulindac; antioncotic, e.g. methotrexate; or hormone, e.g. calcitonin or insulin-like growth factor;

iii) N-aralkyl-amino-alkane-diphosphonic acids as disclosed in EP 371921A (Ciba-Geigy) (disclosed for use in calcium metabolism disorders) having the formula

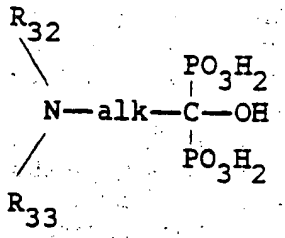


wherein Z_{10} is C_2-C_4aliphatic hydrocarbyl (e.g. alkylene),

R_{30} is phenyl substituted C_4-C_7aliphatic hydrocarbyl,

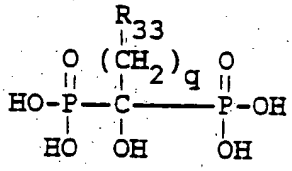
R_{31} is C_1-C_4aliphatic hydrocarbyl;

jjj) N-aralkylamino-1-hydroxyalkane-1,1-diphosphonic acids as disclosed in EP 320455A (Ciba-Geigy) (disclosed for use in calcium metabolism disorders) having the formula



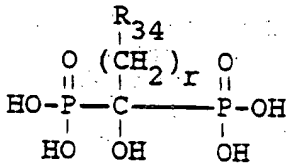
wherein R_{32} ia an aromatically-substituted aliphatic group;
R_{33} is H or monovalent aliphatic group;
alk is a divalent aliphatic group;
provided that when R_{32} is mono-substituted by phenyl, R_{33} is H or when R_{32} has 2 or 3C in the aliphatic portion, R_{33} is an aliphatic group with at most 3C;

kkk) azabicycloalkyl-1-hydroxyalkane-1,1-diphosphonic acids as disclosed in EP 317505A (Ciba-Geigy) (disclosed for use in calcium metabolism disorders) having the structure



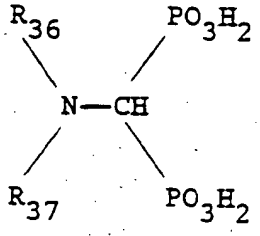
wherein R_{33} is an N-bonded azabicycloalkyl group with 3 to 8-membered rings, such as 3-azabicyclo-(3,1,1,)hept-3-yl, 1,5-dimethyl-3-azabicyclo(3,1,1)-hept-3-yl, 3-azabicyclo(3,2,1)oct-3-yl, 3-azabicyclo-(3,2,2)non-3-yl or 3-azabicyclo(4,2,2)dec-3-yl, and $(CH_2)_q$ is lower alkylene (2 to 4 carbons);

lll) azacycloalkyl-substituted 1-hydroxyalkane-1,1-diphosphonic acids as disclosed in EP 272208A (Ciba-Geigy) (disclosed for use in calcium metabolism disorders) having the formula



wherein R_{34} is an N-bonded, aryl-substituted mono- or diazacycloaliphatic group, such as 3-R_{35}-pyrrolidino, 3- or 4-R_{35}-piperidino or 6-R_{35}-3-azabicyclo(3,1,1)hept-3-yl, wherein R_{35} is phenyl optionally substituted by C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen;

mmm) heteroarylaminomethane diphosphonic acids as disclosed in EP 274346A (Ciba-Geigy) (disclosed for use in calcium metabolism disorders) having the formula



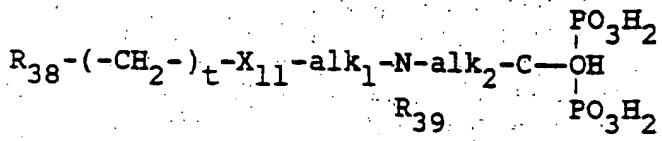
wherein R_{36} is a 5 membered heteroaryl with 2-4 N or with 1-2 N plus an O or S atom, optionally fused to a benzo or cyclohexeno ring;

R_{36} can be C substituted by lower alkyl, phenyl (optionally substituted by lower alkyl, alkoxy and/or halo), lower alkoxy, OH, di(lower alkyl)amino, lower alkylthio and/or halo, and/or N substituted by lower alkyl or phenyl (lower) alkyl (optionally substituted by lower alkyl, lower alkoxy and/or halo);

R_{37} is H or lower alkyl; provided R_{37} is not H if R_{36} is optionally alkyl and/or halo substituted 3-pyrazolyl or 3-isoxazolyl;

examples of R_{36} groups are 2-thiazolyl (optionally substituted by 1 or 2 1-4 C alkyl or phenyl); imidazol-2-yl or benzimidazol-2-yl (optionally 1-substituted by 1-4 C alkyl or phenyl(1-4 C) alkyl); or unsubstituted 2-benzoxazolyl or 2-benzothiazolyl;

nnn) N-substituted aminoalkanediphosphonic acids as disclosed in EP 387194A (Ciba-Geigy) (disclosed for use in calcium metabolism disorders) having the formula



wherein R_{38} is an aromatic residue (such as phenyl, pyridyl or pyrimidyl);

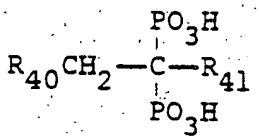
t is 0-3;

X_{11} is O, S (optionally oxidized) or amino (optionally substituted by aliphatic group);

alk_1 and alk_2 are divalent aliphatic groups;

R_{39} is H or monovalent aliphatic group;

ooo) 2-heteroarylethane-1,1-diphosphonic acids as disclosed in Australian Patent 8781453A (Ciba-Geigy) (disclosed for use in calcium metabolism disorders) having the formula

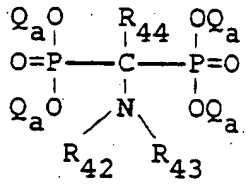


wherein R_{40} is a 5 membered heteroaryl containing either 2-4N atoms or 1-2N atoms and an O or S atom, optionally (a) C-substituted by lower alkyl, aryl, lower alkoxy, OH, di(lower alkyl)amino, lower alkylthio and/or halogen and/or (b) N-substituted by lower alkyl or aryl(lower)alkyl, where aryl in (a) and (b) is phenyl optionally substituted by lower alkyl, lower alkoxy and/or halogen;

R_{41} is H, OH, NH_2, lower alkylthio or halogen;

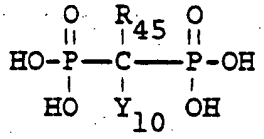
examples of R_{40} groups include imidazolyl, 1,2,4-triazolyl or thiazolyl, optionally C-substituted and/or N-substituted;

ppp) 1-aminoalkane-1,1-diphosphonates as disclosed in U.S. Patent Nos. 3,846,420 and 3,979,385 (Henkel) (disclosed for use as metal ion complexing agents) having the formula



wherein R_{44} is hydrogen, lower alkyl and phenyl; R_{42} and R_{43} are independently hydrogen, alkyl having one to 22 carbon atoms, cycloalkyl having five to six carbon atoms, phenyl, alkylphenyl having seven to 18 carbon atoms, phenylalkyl having seven to 18 carbon atoms and together with the nitrogen atom, piperidino, pyrrolidino and morpholino, and Q_a is hydrogen, alkali metal, ammonium, pyridinium, guanidinium and mono-, di-, and tri-lower-alkanol-ammonium, with the proviso that at least one of R_{42}, R_{43} and R_{44} is other than hydrogen;

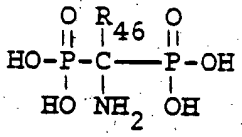
qqq) 1-aminoalkane-1,1-diphosphonic acids as disclosed in U.S. Patent No. 3,899,496 (Henkel) having the formula



wherein R_{45} represents a hydrogen atom or an alkyl residue with 1 to 12 carbon atoms, a phenyl group, a cyclohexyl group, a phenylalkyl group with 7-12 carbon atoms, a piperidinyl group, a carboxyalkyl group with 2-12 carbon atoms, or a carbalkoxy alkyl group with 3-12 carbon atoms; and

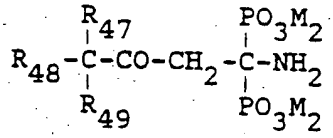
Y_{10} represents an NH_2 group, a piperidino group, a morpholino group or a NR_xR_y group, wherein R_x and R_y represent alkyl residues with 1 to 4 carbon atoms;

rrr) aminophosphonic acids as disclosed in U.S. Patent No. 3,303,139 (Henkel) (disclosed for use as metal ion complex formers) having the formula



wherein R_{46} is a saturated or unsaturated aliphatic radical having 1-10 carbon atoms or a phenyl- or benzyl-radical;

sss) 3-alkyl-3-oxo-1-amino-propane-1,1-diphosphonic acids as disclosed in DE 3611522A (Henkel) (disclosed for use in inhibiting growth of bacteria) having the formula

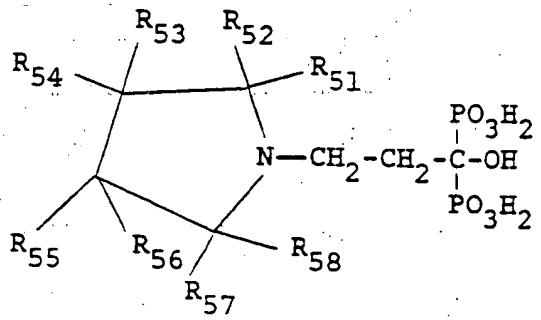


wherein R_{47} is optionally branched 1-8C alkyl;

R_{48} and R_{49} are each methyl or ethyl;

M is H or a cation of a water-soluble base;

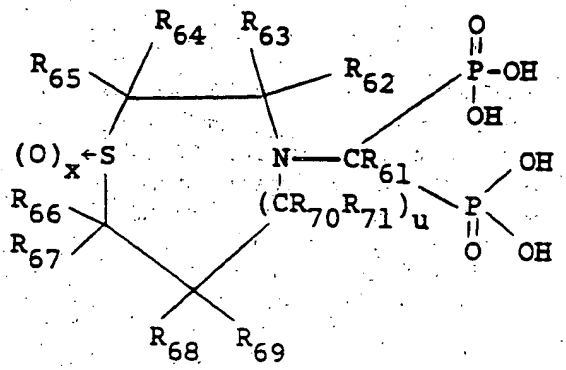
ttt) N-heterocyclic propylidene-1,1-bis-phosphonic acids as disclosed in WO 89/09775 (PCT/DK89/00071) (Leo Pharmaceutical Products) (disclosed for use in calcium metabolism disorders) having the formula



in which R_{51}-R_{58} can be the same or different and stand for hydrogen or a straight or branched alphatic C_1-C_{10} hydrocarbon radical; and

R_{53} when taken together with either R_{51} or R_{55} can form a saturated aliphatic 5-, 6- or 7-membered ring, which may be substituted with one or more C_1-C_4-alkyl radicals;

uuu) thiomorpholinylmethylene-bisphosphonic acids as disclosed in WO 8703-598A (Leo Pharmaceuticals) (disclosed for use in reducing bone resorption and stimulating bone alkaline phosphatase) having the formula



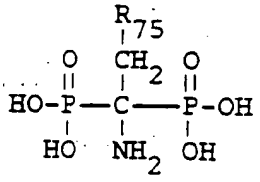
wherein R_{61}-R_{71} are independently H, straight, branched or alicyclic 1-10C hydrocarbyl, aryl or aryl-(1-4C)alkyl;

x is 0 or 1;

u is 0, 1 or 2 or

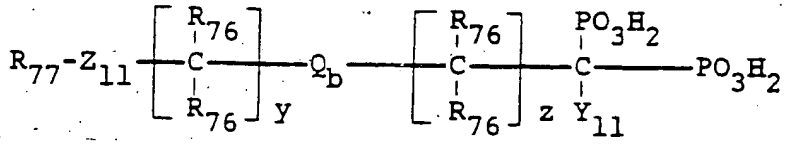
$^{R}62$ + $^{R}64$ may complete a 5- to 7-membered saturated aliphatic ring, optionally substituted by one or more 1-4C alkyl groups;

vvv) 1-aminoalkane-1,1-diphosphonic acids as disclosed in U.S. Patent No. 4,100,167 (Nalco Chemical) (disclosed for use as anti-corrosives) having the formula



wherein R_{75} is alkyl, aryl, arylalkyl (including phenyl substituted with a sulfonic acid group, halo or pyridyl);

www) heterocycle-substituted diphosphonic acids as disclosed in EP 274158A (Norwich Eaton) (disclosed for use in calcium or phosphate metabolism disorders and as antiplague agents, herbicides) having the formula



wherein Z_{11} is a N-containing 6-membered ring heterocycle moiety selected from piperidinyl, diazinyl or triazinyl;

Q_b is a covalent bond, O, S or NR_{76};

y, x and y + x are integers of 0-10;

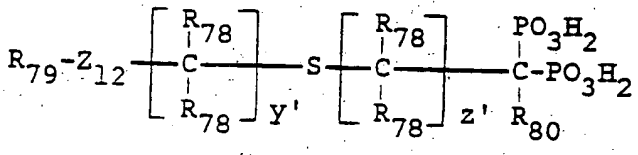
Y_{11} is H, halogen, 1-6C alkyl, phenyl, benzyl, hydroxy or its ester derived from a 1-6C carboxylic

acid, unsubstituted amino or its amide derived from a 1-6C carboxylic acid, amino substituted with one alkyl having 1-6C or its amide derived from a 1-6C carboxylic acid, di(1-6C alkyl)amino, tri(1-6C alkyl)-ammonium, CO_2H or its salts or esters derived from 1-6C alcohols, or its amide optionally substituted with one or two 1-6C alkyl groups, except when n = 0 and Q_b = O, S or N, then Y_{11} is H, 1-6C alkyl, phenyl, benzyl, or Co_2H or its salts or the esters derived from 1-6C alcohols or its amide optionally substituted with one or two 1-6C alkyl groups;

R_{76} is H, methyl, ethyl or propyl;

R_{77} is one or more substituents selected from H, halogen, 1-3C alkyl, unsubstituted amino and its amide derived from a 1-3C carboxylic acid, mono(1-3C alkyl) amino and its amide derived a 1-3C carboxylic acid, di(1-3C alkyl)amino, tri(1-3C alkyl)ammonium, hydroxy or its ester derived from a 1-3C carboxylic acid, ether having 1-3C, CO_2H and its salts and esters derived form 1-3C alcohols, its amide optionally substituted with one or two 1-3C alkyl groups and NO_2;

xxx) N-heterocyclyl thio alkane diphosphonic acids as disclosed in EP 230068A (Norwich Eaton) (disclosed for use in calcium and phosphate metabolism disorders) having the structure



wherein Z_{12} is a 6-membered aromatic ring containing ≥ 1 N atom(s); where:

the ring is optionally substituted by (optionally substituted, optionally unsaturated) 1-6C alkyl, (optionally substituted) aryl, (optionally substituted) benzyl, OH, halogen, carbonyl, alkoxy, NO_2, $CONH_2$, (optionally substituted) NH_2 and/or carboxylate;

R_{78} is H or (optionally substituted, optionally unsaturated) 1-4C alkyl;

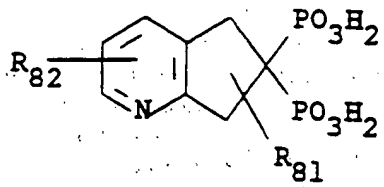
R_{79} is H, (optionally substituted, optionally unsaturated) 1-6C alkyl, (optionally substituted) aryl, (optionally substituted) benzyl, OH, halogen, carbonyl, alkoxy, NO_2, $CONH_2$, (optionally substituted) amino or carboxylate;

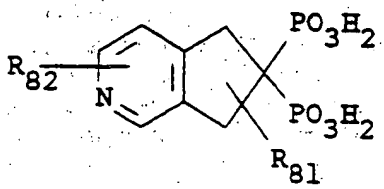
R_{80} is H, (optionally substituted) NH_2, $CONH_2$, OH, alkoxy, halogen, carboxylate, (optionally substituted, optionally unsaturated) 1-6C alkyl;

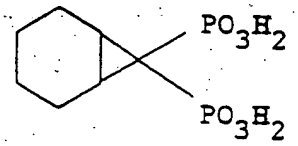
examples of Z_{12} are pyridine, pyridazine, pyrimidine or pyrazine ring;

y' + z' is 0 to 5;

zzz) cyclic diphosphonic acids as disclosed in EP 304962A (Procter & Gamble) (disclosed for use in calcium and phosphate metabolism disorders) having the formula

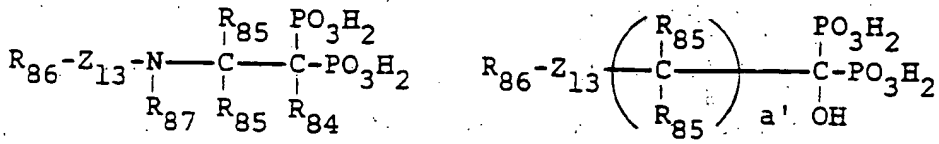






R_{81} and R_{82} are each one or more substituents selected from H, optionally substituted saturated or unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, amimo, OH, halogen, optionally substituted amino, amido, COOH, carbonyl, carboxylate, alkoxy and NO_2;

a^4) heterocyclyl-alkane-diphosphonic acids as disclosed in Australian Patent 8551534A (Procter & Gamble) (disclosed for use in resorption of bone tissue) having the formula



wherein Z_{13} is pyridine, pyridazine, pyrimidine or pyrazine ring; this ring is optionally substituted by optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, oxo, alkoxy, NO_2, amido, optionally substituted NH_2 or carboxylate;

R_{84} is H, optionally substituted NH_2, amido, OH, alkoxy, halogen, carboxylate, optinally substituted optionally unsaturated 1-6C alkyl, optionally substituted aryl or optionally substituted benzyl;

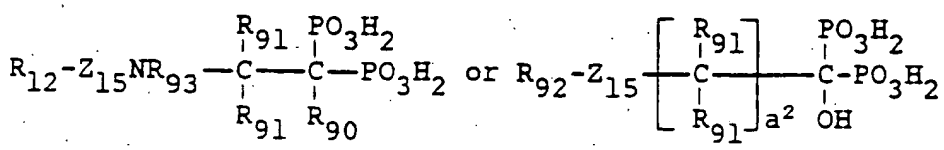
R_{85} is H or optionally substituted optionally unsaturated 1-4C alkyl;

, R_{86} is one or more of H, optionally substituted optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, oxo, alkoxy, NO_2, amido, optionally substituted NH_2 or carboxylate;

R_{87} is H, optionally substituted optionally unsaturated 1-4C alkyl or acyl;

a' is 1-5;

b^4) geminal diphosphonates as disclosed in EP 186405A (Procter & Gamble) (disclosed for use in calcium and phosphate metabolism disorders) having the strucuture



wherein Z_{15} is a 6 membered aromatic ring containing 1 or more N atoms such as pyridine, pyridazine, pyrimidine or pyrazine which ring may be substituted with one or more optionally substituted, optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, carbonyl, alkoxy, NO_2, amido, optionally substituted amino or carboxylate;

R_{90} is H, optionally substituted amino, amido, OH, alkoxy, halogen, carboxylate, optionally substituted, optionally unsaturated 1-6C alkyl, optionally substituted aryl or optionally substituted benzyl;

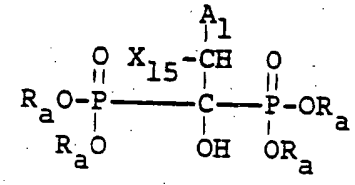
R_{91} is H or optionally substituted optionally unsaturated 1-4C alkyl;

R_{92} is H or one or more substituents selected from optionally substituted, optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, carbonyl, alkoxy, NO_2, amido, optionally substituted amino or carboxylate;

R_{93} is H, optionally substituted, optionally unsaturated 1-4C alkyl or acyl;

a^2 is 1 to 5;

C[4]) diphosphonic acid derivatives as disclosed in U.S. Patent No. 4,503,049 (Schering A.G.) (disclosed for use as anti-inflammatory agents) having the structure

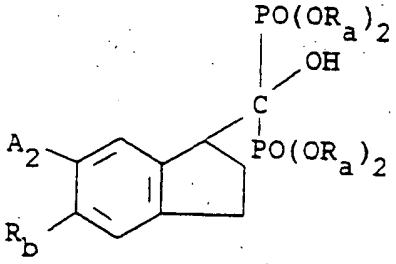


wherein R_a is hydrogen, an alkali metal atom, an alkaline earth metal atom, or alkyl of 1-4 carbon atoms,

X_{15} is hydrogen, methyl, or ethyl, and

A_1 is phenyl substituted in the para-position by isobutyl, cyclohexyl, alkoxy, or 1-pyrrolinyl and, optionally substituted additionally in the meta-position by fluorine or chlorine, or phenyl substituted in the meta-position by benzoyl or phenoxy, or phenyl substituted in the ortho-position by 2,4-dichlorophenoxy or 2,6-dichlorophenylamino;

diphosphonic acid derivatives of the sturcture

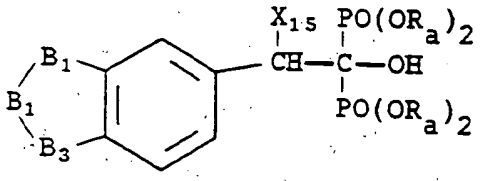


wherein R_a is as defined above;

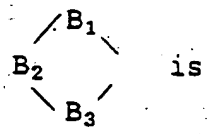
R_b is cyclohexyl or cyclopentylmethyl; and

A_2 is hydrogen or chlorine;

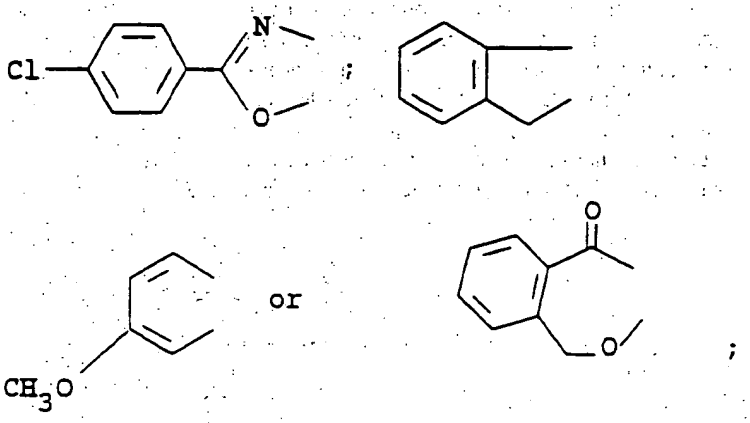
diphosphonic acid derivatives of the formula



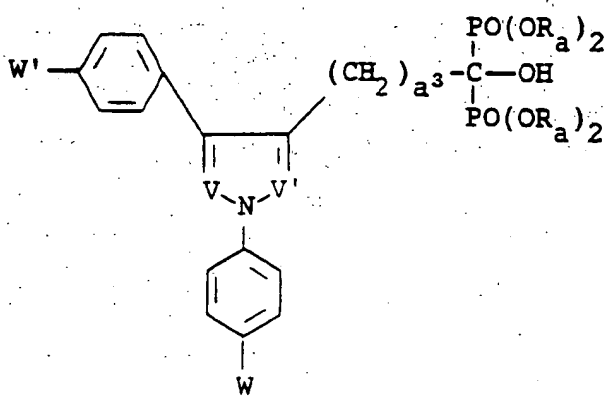
wherein R_a and X_{15} are as defined above, and



is



diphosphonic acid derivatives of the formula

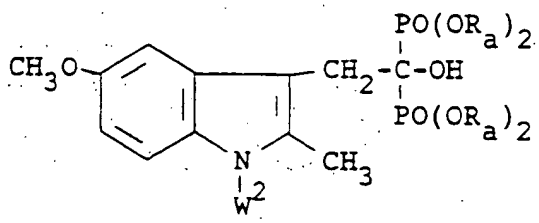


wherein a^3 is 1, 2 or 3,

R_a is as defined above,

W and W' are identical or different, and each is hydrogen, fluorine or chlorine, and

one of V and V' is nitrogen and the other is a methyne residue optionally substituted by a phenyl group; and diphosphonic acid derivatives of the formula

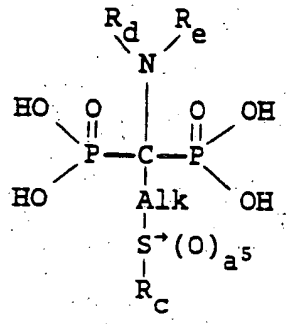


wherein R_a is as defined above, and

W^2 is p-chlorobenzoyl or cinnamoyl; or throughout, when R_a is H, a physiologically acceptable salt

thereof with an organic base;

d^4) methylenediphosphonic acids as disclosed in U.S. Patent No. 4,876,247 (Sanofi) (disclosed for use as an antirheumatic) having the formula



wherein R_c represents:

a C_1-C_6 alkyl group,

a C_5-C_7 cycloalkyl group,

a phenyl group optionally monosubstituted or poly-substituted by a halogen, a C_1-C_6 alkyl group or a trifluoromethyl group, or

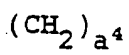
a 5-membered or 6-membered heterocycle containing 1 or 2 heteroatoms chosen from nitrogen and sulfur,

Alk denotes a linear or branched C_1-C_6 alkylene group,

R_d represents hydrogen, a C_1-C_6 alkyl group or a -$CONH_2$ group,

R_e represents hydrogen, a C_1-C_6 alkyl group, a benzyl group or a phenyl group optionally substituted by chlorine or methyl groups; or alternatively

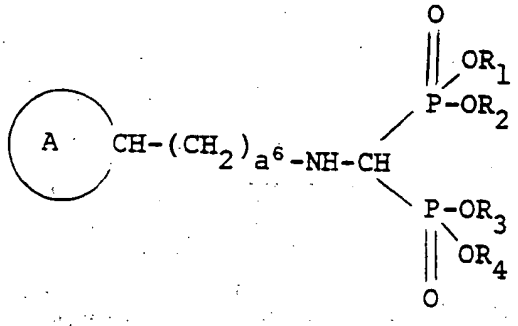
R_d and R_e taken together, represent a



group, in which a^4 is 4 or 5, and

a^5 represents 0 or the integer 1 or 2.

e^4) aminomethylene-bisphosphonic acids as disclosed in EP 337706A (Yamanouchi Pharm) (disclosed for use in inhibiting bone resportion, and for its anti-inflammatory, antirheumatic and analgesic activities) having the structure



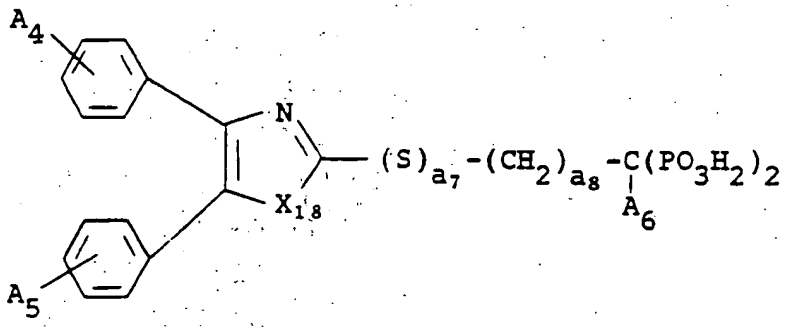
wherein R_1-R_4 is H or 1-5C alkyl;

a^6 is 0-4;

Ring A is 5-8-cycloalkenyl, bicycloheptyl, bicycloheptenyl or 4-7C saturated heterocyclyl containing O, S, SO or SO_2;

f^4) diphenylazolediphosphonic acids as disclosed in Japanese Patent 210445 (Yamanouchi Pharm)

(disclosed for use as anti-inflammatory, antipyretic and analgesic agents) having the structure



wherein A_4 and A_5 are the same or different and are H, OH, lower alkoxy or halogen;

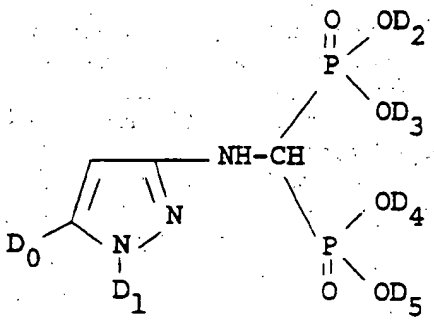
A_6 is H or OH:

X_{18} is O, S or NH;

a_7 is 0 or 1;

A_8 is 0 or an integer of 1-6;

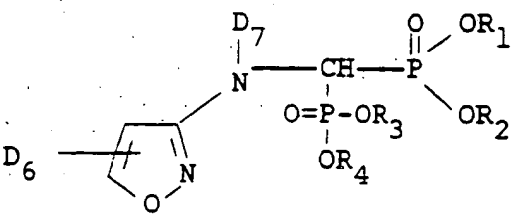
g[4]) (pyrazolylamino)methylene-bis-(phosphonic acids) as disclosed in Japanese Patent 086857 (Yamanouchi Pharm) (disclosed for use as bone resorption inhibitors) having the formula



(wherein D_0 is H or alkyl;

D_1 to D_5 is H or lower alkyl);

h[4]) isoxazolyl-containing bisphosphonic acids as disclosed in EP 282320A (Yamanouchi Pharm) (disclosed for use as bone resorption inhibitors and in arthritis) having the formula



wherein D_6 is H, 1-10C alkyl, 3-10C cycloalkyl, phenyl, 2-10C alkenyl (optionally substituted by phenyl) or phenyl(1-5C)alkyl (optionally ring-substituted by a 1-5C alkoxy);

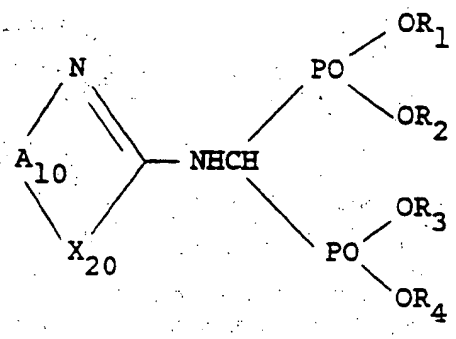
D_7 is H or 2-6C alkanoyl; and

R_1-R_4 is H or 1-5C alkyl;

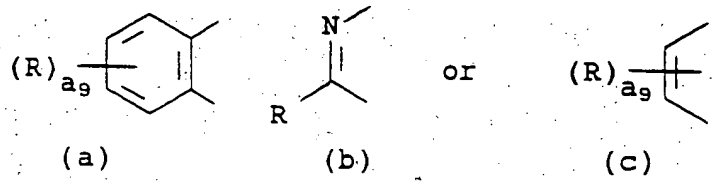
provided that when D_6 is methyl, ethyl, isopropyl or tert-butyl, at least one of D_7, R_1, R_2, R_3 or R_4 is other than H;

i[4]) azole-amino methylene bisphosphonic acids as disclosed in EP 282309A (Yamanouchi Pharm)

(disclosed for use as bone resorption inhibitors) having the sturcture

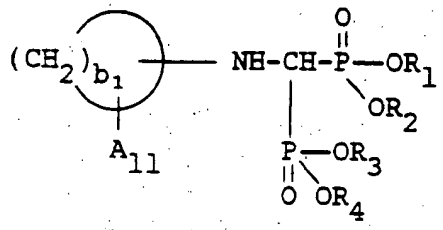


wherein A_{10} = a group of formula (a)-(C):



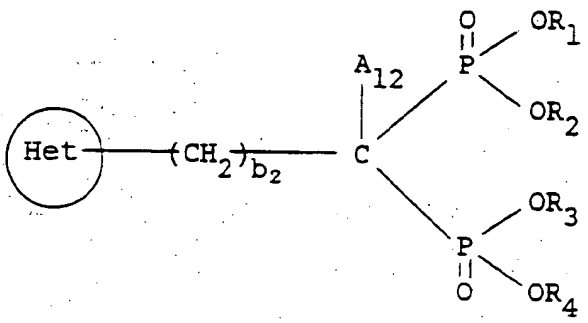
R is H, halogen, 1-5C alkyl or phenyl;
a_9 is 1 or 2;
X_{20} is O, S or NH;
R_1-R_4 is H or 1-5C alkyl;

j[4]) cycloalkyl:amino-methylene-bis:phosphonic acids having the formula

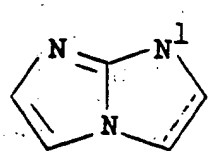


wherein A_{11} and R_1 - R_4 are H or 1-5C alkyl;
b_1 is 3-10; provided that A_{11} is 1-5C alkyl when R_1 - R_4 is H and b_1 is 5 or 6;

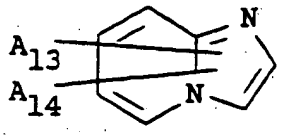
k[4]) heterocyclic bisphosphonic acids as disclosed in EP 354806A (Yamanouchi Pharm) (disclosed for use in bone resorption) having the formula



wherein ring Het is a group of formula (A) or (B):



(A)



(B)

the dotted line represents optionally double bond;

A_{13}, A_{14} are independently H, 1-5C alkyl, halogen or OH;

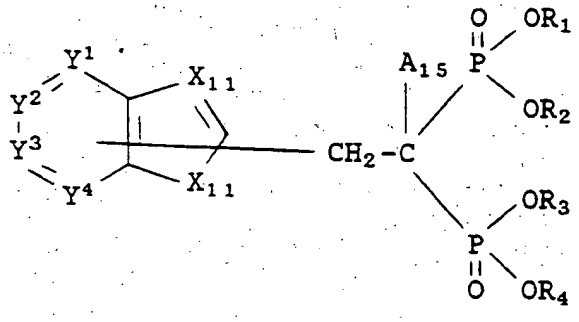
A_{12} is H or OH;

R_1, R_2, R_3, R_4 are H or 1-5C alkyl;

b_2 is 0 or 1; provided that b_2 is 1 when ring Het is (A); and

A_{12} is OH when ring Het is (B).

[4]) imidazo- or pyrrolo-pyridine substituted bisphosphonic acids as disclosed in Japanese Patent 200462 (Yamanouchi Pharm) (disclosed for use as bone resorption inhibitors) having the structure



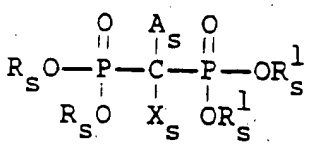
wherein A_{15} is H or OH;

R_1-R_4 is H or lower alkyl;

X_{11} is both N or one is N and the other is CH;

one of Y^1-Y^4 is N and the rest are CH.

In another aspect of the present invention, a pharmaceutical composition is provided for inhibiting cholesterol biosynthesis and thereby reducing plasma (or serum) cholesterol by inhibiting the enzyme squalene synthetase wherein bisphosphonate compounds as described above are employed or compounds as disclosed in U.S. Patent Nos. 4,309,364 and 4,416,877 and UK Patent 2,079,285A, all to Bentzen et al and assigned to Symphar S.A. (hereinafter referred to as the Symphar patents) are employed. Thus, the pharmaceutical compositions of the invention inhibit squalene synthetase by containing compounds disclosed in the Symphar patents including diphosphonates of the formula



wherein R_s and R_s^1 are the same or different and are H, methyl or ethyl, wherein at most only one of R_s and R_s^1 is methyl or ethyl;

X_s is H, OH, $OCOCH_3$ or NH_2;

A_s is t-butyl; Y_s-C_6H_4-; Y_s-C_6H_4-O-$C(CH_3)_2$-; Y_s-C_6H_4-$C(CH_3)_2$-; Y_s-C_6H_4-CO-C_6H_4; Y_s-C_6H_4-$(CH_2)_{ns}$- and Y_s-C_6H_4-O-$(CH_2)_{ns}$-

where ns is 1 to 6 and

Y_s is H, CH_3, halogen, OC_{1-20} alkyl.

It will be appreciated that C_6H_4 in the above groups represents a phenylene group.

Examples of compounds of the Symphar type suitable for use in the preparation of the pharmaceutical compositions for inhibiting squalene synthetase include

tetramethyl 1(p-chlorophenyl)methane-1-hydroxy 1,1-diphosphonate,

tetramethyl 2,2-dimethyl 2-(p-chlorophenoxy)ethane 1-hydroxy-1,1-diphosphonate,

tetramethyl 1-[4(4'-chlorobenzoyl)phenyl]-methane 1-hydroxy 1,1-diphosphonate,

dimethyl 1[(dimethoxyphosphinyl)p-chlorobenzyl]phosphate,

dimethyl [1(dimethoxyphosphinyl) 2,2-dimethyl 2-phenyl]-ethyl phosphate,

dimethyl [1(dimethoxyphosphinyl)2,2-dimethyl 2(p-chlorophenyl] ethyl phosphate,

tetramethyl 4-phenylbutylidene, 1,1-diphosphonate.

More preferred are compounds of formula I wherein one of R^5 and R^6 is a lipophilic group which is optionally substituted alkyl, optionally substituted alkenyl or optionally substituted aryl, and the other of R^5 and R^6 is hydrogen, lower alkyl or halogen.

In the pharmaceutical compositions of the invention bisphosphonate compounds are used which inhibit cholesterol biosynthesis by inhibition of de novo squalene production. These bisphosphonate compounds (which are described in detail hereinbefore) inhibit the squalene synthetase enzyme and, in addition, some of these compounds inhibit other enzymes in the pathway from isopentenyl diphosphate to squalene, that is, farnesyl diphosphate synthetase and isopentenyl diphosphate-dimethylallyl diphosphate isomerase.

Thus, the pharmaceutical compositions of the invention are useful in treating atherosclerosis to inhibit progression of disease and in treating hyperlipidemia to inhibit development of atherosclerosis. In addition, they may be employed to increase plasma high density lipoprotein cholesterol levels.

Inasmuch as the pharmaceutical compositions of the invention employ squalene synthetase inhibitors, they may also be useful in inhibiting formation of gallstones, treating tumors, lowering blood pressure, lowering blood sugar, treating diabetes mellitus, treating inflammation, for diuretic therapy, for inotropic therapy, for anti-arthritic (antirheumatic) therapy, in treating other diseases of calcium and phosphate metabolism including treatment of bone resorption, Paget's disease, osteoporosis, calcification of joints, implants and metastasis, as antitartar and anti-calculus therapy by means of toothpastes and mouthwashes, treating various stones and calculi, treating sickle cell anemia, treating hypoxia and ischemic tissue, and as anti-ameobal therapy, as well as in carrying out diagnostic techniques wherein the squalene synthetase inhibitors are employed in complexes with technetium-99m and radioiodinated derivatives.

The pharmaceutical compositions of the invention may also be employing the bisphosphonate squalene synthetase inhibitor in combination with an anti-hyperlipoproteinemic agent such as probucol and/or with one or more serum cholesterol lowering agents such as Lopid (gemfibrozil), bile acid sequestrants such as cholestyramine, colestipol, polidexide (DEAE-Sephadex) as well as clofibrate, nicotinic acid and its derivatives, neomycin, p-aminosalicyclic acid, bezafibrate and the like and/or one or more HMG CoA reductase inhibitors such as lovastatin, pravastatin, velostatin or simvastatin.

The above compounds to be employed in combination with the squalene synthetase inhibitor of the invention may also be used in amounts as indicated in the Physicians' Desk Reference (PDR).

The compounds employed in the pharmaceutical compositions of the invention may also be employed with sodium lauryl sulfate or other pharmaceutically acceptable detergents to enhance oral bioavailability of such compounds.

Inhibition of squalene synthetase may be measured by the following procedure.

Rat liver microsomal squalene synthetase activity is measured using farnesyl diphosphate as substrate and quantitating squalene synthesis using gas chromatographic analysis. The assay was developed by modifying conditions originally described by Agnew (Methods in Enzymology 110:357, 1985).

Preparation of Rat Liver Microsomes:

Livers are dissected from 2 or 3 decapitated Sprague Dawley rats and are quickly transferred to ice cold buffer (potassium phosphate, 0.05 M, (pH 7.4); $MgCl_2$, 0.004 M; EDTA, 0.001 M; and 2-mercaptoethanol 0.01 M) and rinsed thoroughly. The livers are minced in cold buffer (2.0 ml/g) and homogenized using a Potter-Elvejhem homogenizer. The homogenate is centrifuged at 5,000 x g, 10 minutes (4°C), and the supernatant poured through 2 layers of cheese cloth. The supernatant is then centrifuged at 15,000 x g for 15 minutes (4°). Again the supernatant is filtered through 2 layers of cheese cloth, and centrifuged a third time at 100,000 x g for 1.0 hour at 4°C. Following centrifugation the microsomal pellet is resuspended in a volume of buffer equivalent to 1/5 the volume of the original homogenate, and homogenized in a ground

glass homogenizer. Aliquotted microsomes are frozen at -80 ° C, and retain activity for at least two months.

Enzyme Assay:

Reaction Mixtures are prepared in 50 ml round bottom pyrex glass tubes with tight-fitting, teflon-lined, screw caps. Tubes are cooled to 4 ° C, and the following components are added in sequence:

1. Potassium phosphate buffer (0.275 M, pH 7.4)	0.36 ml
2. KF (55 mM)	0.36 ml
3. NADPH (5.0 mM, freshly prepared)	0.36 ml
4. H_2O (or H_2O + test compound)	0.16 ml
5. $MgCl_2$ (27.5 mM)	0.36 ml
6. Microsomal Enzyme (0.48 mg microsomal protein in homogenization buffer) (15 µl prep.) 4/23/86	0.20 ml
	1.8 ml

This mixture is equilibrated under N_2 at 4 ° C for 5-15 minutes. Reaction mixtures are then warmed to 30 ° C, and the enzyme reaction initiated by adding 0.2 ml of farnesyl pyrophosphate (219 µM) prepared in H_2O. Each tube is again overlayered with N_2, and incubated at 30 ° C for 60 minutes. The reaction is stopped by the addition of 1.0 ml KOH (40%). Ethanol (95%) (spectral grade) (1.0 ml) is added to each tube. Docosane (5 nmoles in hexane) is added to each tube as an internal standard. The mixture is saponified at 65 ° C for 30 minutes. The tubes are cooled to room temperature and extracted twice with 10.0 ml spectral grade hexane.

The upper organic phase fractions are pooled in glass 20.0 ml scintillation vials and reduced in volume to ≈ 1.0 ml under a stream of N_2. The sample is then transferred to acid-washed, conical bottom, glass (1.0 ml) microvials, and brought to dryness under N_2. The residue is resuspended in 50 µl hexane (spectral grade), and these samples are spun at 1000 rpm at room temperature for 10 minutes. Following centrifugation approximately 40 µl of supernatant is transferred to 100 µl acid-washed microvials with septa/crimp-top caps (compatible with the Hewlett-Packard GC auto injector).

Gas Chromatography:

Two µL of each sample is injected onto a fused silica megabore DB-17 column (15 M x 0.525 mm) (J&W Scientific) using a splitless mode of injection. Gas flow rates are listed below:

Make up gas (helium)	20 ml/min.
Air	400 ml/min.
Hydrogen	30 ml/min.
Carrier (helium)	15 ml/min.
Septum purge vent	5 ml/min. (Septum purge off 0.00 min., on at 0.5 min.)

The injector temperature is 200 ° C, and the FID detector temperature is set at 270 ° C. Oven temperature is programmed through a two ramp sequence as follows:

Oven:

Initial temperature 180 ° C, initial time 10 minutes Ramp one: 20 ° C/minute

Second temperature 250 ° C, second time 10 minutes Ramp two: 20 ° C/minute

Third temperature 260 ° C, third time 10 minutes (Equilibration time 1.0 minute)

Using this gas chromatographic system, docasane (internal standard) has a retention time of 3.6-3.7 minutes, and squalene has a retention time of 14.7-14.9 minutes. The amount of squalene in each reaction mixture is determined by obtaining the areas under the squalene and docasane peaks and using the following formula to calculate the amount of squalene (nmoles) in the total reaction mixture.

$$\text{Squalene (nmoles/reaction} = 5.0 \text{ (nmoles docasane mixture)} \times \text{internal standard)}$$

$$\frac{\text{Squalene Peak Area}}{\text{Docasane Peak Area}} \times RR^*$$

*RR = Response Ratio [Docasane/Squalene]

*RR = 0.56

Compounds Testing:

Compounds are dissolved in H_2O and added to reaction mixtures prior to addition of farnesyl pyrophosphate substrate. All reaction mixtures are run in duplicate, at several concentrations. Additionally, all compound I_{50} values are derived from composite dose response data.

In carrying out the invention, a pharmaceutical composition will be employed containing at least one bisphosphonate squalene synthetase inhibitor in association with a pharmaceutical vehicle or diluent. The pharmaceutical compostion can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds can be administered to mammalian species including humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations. The dose for adults is preferably between 200 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

A typical capsule for oral administration contains bisphosphonate squalene synthetase inhibitor (250 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

A typical injectible preparation is produced BY asceptically placing 250 mg of sterile bisphosphonate squalene synthetase inhibitor into a vial, asceptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 ml of physiological saline, to produce an injectible preparation.

The following Examples illustrate the preparation of preferred bisphosphonate compounds which may be employed in the pharmaceutical compositions of the invention for inhibiting cholesterol biosynthesis by inhibiting de novo squalene production.

All temperatures are reported in degrees Centigrade.

^1H and ^{13}C chemical shifts are reported as δ-values with respect to Me_4Si ($\delta = 0$). ^{31}P spectra were measured on a JEOL FX90Q FT-NMR spectrometer, at 36.2 MHz, utilizing the ^1H decoupled mode. The ^{31}P data were obtained using 85% H_3PO_4 as an external reference ($\delta = 0$). Coupling constants J are reported in Hz. Chemical ionization mass spectra (CI-MS) were determined with a Finnigan TSQ-4600 instrument equipped with a direct exposure probe using the indicated reagent gases. Fast atom bombardment mass spectra (FAB-MS) were recorded on a VG Analytical ZAB-2F spectrometer. Ions were sputtered (8keV Xe) from a matrix containing dithiothreitol, dithioerythritol, DMSO, glycerol and water.

All reactions were carried out under an atmosphere of dry argon or nitrogen. The following reagents and solvents were distilled prior to use from the indicated drying agents, where applicable: CH_2Cl_2, 2,4,6-collidine, and diisopropylamine (CaH_2); THF and diethyl ether (K, benzophenone); N,N-diethyltrimethylsilylamine and oxalyl chloride. Benzene was passed through neutral alumina (activity I) and stored over 4A-molecular sieves. Lithium bromide was dried at 100°C over P_2O_5.(E,E)-Farnesol was purchased from Aldrich Chemical Company.

TLC was performed on E. Merck Silica Gel 60 F-254 plates (0.25 mm) or E. Merck Cellulose F plates (0.1 mm). Flash chromatography was carried out using E. Merck Kieselgel 60 (230-400 mesh).

Reverse-phase chromatographic purification of salts or mixed ester-salts was carried on CHP20P gel or SP207SS gel, a highly porous, polystyrene-divinyl benzene copolymers available from Mitsubishi Chemical Industries. The indicated general procedure was followed: An FMI Model RP-SY pump was utilized for

solvent delivery. A column of CHP20P (2.5 cm diameter, 12-22 cm height) was slurry packed and washed with water (500-1000 mL), and a basic, aqueous solution of the crude salt was applied to the top of the column. Typically, the column was eluted with water, followed by a gradient composed of increasing concentrations of acetonitrile or methanol in water. The gradient was created by placing the tip of a tightly stoppered separatory funnel containing 300-500 mL of the organic solvent, or an aqueous-organic mixture, just beneath the surface of a reservoir containing 300-500 mL of pure water. To start the gradient, the stopcock of the separatory funnel was opened, so that as the solvent was withdrawn by the pump from the reservoir, it was replaced with the solvent from the separatory funnel. HPLC-grade solvents and Lectrostill steam distilled water were employed. Fractions were collected (10-15 mL each) at a flow rate of 5-10 mL per minute. Those fractions that contained pure product as judged by TLC were pooled, the organic solvents were evaporated and the aqueous residue was lyophilized to dryness.

Example 1

(Undecylidene)bisphosphonic acid, trisodium salt

A. (Undecylidene)bisphosphonic acid, tetraethyl ester

A suspension of 0.29 g (12.07 mmol) of NaH in 13 mL of dry DMF at 0°C under argon was treated with 3.45 g (11.98 mmol) of tetraethyl methylenediphosphonate over 0.3 hours to give a yellow solution. The reaction was allowed to warm to room temperature and stir for 0.5 hours when 2.70 g (10.06 mmol) of 1-iododecane (Aldrich Chemical) was added in one portion. The reaction mixture was stirred for 12 hours at room temperature when the reaction was quenched with 7.0 mL of water. The resulting emulsion was diluted with water (100 mL) and extracted with ethyl acetate (200 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to provide a thick oil. The oil was purified by flash chromatography on 250 g of silica gel packed, loaded, and eluted with ethyl acetate (500 mL), followed by 1.5 L of 1:9 ethanol/ethyl acetate to provide 2.40 g (56%) of title ester as a pale yellow oil.
TLC Silica gel (1:9 ethanol:ethyl acetate) $R_f = 0.50$.
IR (CCl_4 film) 2980, 2926, 2854, 1445, 1251, 1028, 968 cm^{-1}.
^1H NMR ($CDCl_3$, 270 MHz): δ 4.12 (m, 8H), 2.30 (tt, 1H, J = 24.2, 6.0 Hz), 1.90 (m, 2H), 1.57 (m, 2H), 1.34 (t, 12H, J = 7.0 Hz), 1.26 (m, 14H), 0.88 (t, 3H, J = 6.5 Hz) ppm.
Mass Spec. (CI, NH_3, + ions) m/e 429 (M + H).

B. (Undecylidene)bisphosphonic acid, trisodium salt

To a stirred solution of 1.00 g (2.33 mmol) of Part A ester in 10 mL of dichloromethane at 0°C was added 1.70 mL (11.68 mmol) of iodotrimethylsilane. The reaction was allowed to stir at room temperature for 12 hours when the solvent was evaporated and the residue pumped (~ 1 mm pressure) for 0.5 hour. The remainder was dissolved by adding 21 mL (10.5 mmol) of 0.5 N NaOH solution and freeze dried. The crude white solids were purified by MPLC on a column of CHP20P gel (700 mL of gel) eluting with water (1.5 L). The soapy fractions were combined, reduced to a 125 mL volume and filtered through a nylon membrane (pore size 0.2 μm). The filtrate was lyophilized to provide 0.56 g (63%) of title compound as a white lyophilate.
IR (KBr) 3668, 3375, 2957, 2924, 2872, 1641, 1468, 1155, 1107, 886 cm^{-1}.
^1H NMR (D_2O, 400 MHz): δ 1.70 (m, 3H), 1.45 (m, 2H), 1.25 (m, 14H), 0.79 (t, 3H, J = 6.9 Hz) ppm.
Mass Spec. (FAB) m/e 405 (M + Nz), 383 (M + H), 365 (M-H_2O + H), 361 (M-Na + 2H).

Anal. Calc'd for $C_{11}H_{23}O_6Na_3P_2$ + 1.00 H_2O			
Found:	C, 33.01; C, 32.83;	H, 6.30; H, 6.26;	P, 15.48 P, 15.20.

Example 2

(Pentadecylidene)bisphosphonic acid, tripotassium salt

A. (Pentadecylidene)bisphosphonic acid, tetraethyl ester

A suspension of 0.26 g (11.0 mmol) of NaH in 12 mL of dry DMF at 0°C under argon was treated with 3.00 g (11.00 mmol) of tetraethyl methylenediphosphonate over 0.3 hours to give a yellow solution. The reaction was allowed to warm to room temperature and stir for 0.5 hours when 2.77 g (10.00 mmol) of 1-bromotetradecane (Aldrich Chemical) was added in one portion. The reaction mixture was stirred for 12 hours at room temperature when the reaction was quenched with 7.0 mL of water. The resulting emulsion was diluted with water (100 mL) and extracted with ethyl acetate (200 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to provide a thick oil. The oil was purified by flash chromatography on 250 g of silica gel packed, loaded and eluted with ethyl acetate (500 mL) followed by 1.5 L of 1:9 ethanol/ethyl acetate to provide 2.70 g (56%) of title ester as a pale yellow oil.
TLC Silica gel (1:9 ethanol:ethyl acetate) $R_f = 0.50$.
IR (CCl_4 film) 2978, 2924, 2854, 1467, 1445, 1251, 1165, 1098, 1028, 968 cm^{-1}.
^1H NMR ($CDCl_3$, 270 MHz): δ 4.18 (m, 8H), 2.26 (tt, 1H, J = 24.2, 5.9 Hz), 1.90 (m, 2H), 1.57 (m, 2H), 1.34 (t, 12H, J = 7.0 Hz), 1.26 (m, 22H), 0.88 (t, 3H, J = 6.2 Hz) ppm.
Mass Spec. (Cl-NH_3, + ions) m/e 502 (M + NH_4), 485 (M + H).

B. (Pentadecylidene)bisphosphonic acid, tripotassium salt

To a stirred solution of 2.40 g (4.95 mmol) of Part A ester in 10 mL of dichloromethane at 0°C was added 3.30 mL (25.0 mmol) of bromotrimethylsilane. The reaction was allowed to stir at room temperature for 12 hours when the solvent was evaporated and the residue pumped (~ 1 mm pressure) for 0.5 hours. The remainder was dissolved by adding 15 mL (15.0 mmol) of 1 N KOH solution. The crude solution was purified by MPLC on a column of CHP20P gel (700 mL of gel) eluting with water (1.0 L) followed by 20% acetonitrile in water (2.0 L). The pure fractions were combined, reduced to a 225 mL volume and filtered through a nylon membrane (0.2 µm pore size). The filtrate was lyophilized to provide 1.71 g (71%) of title salt as a white lyophilate.
IR (KBr) 3668, 3136, 2920, 2852, 1641, 1467, 1114, 868 cm^{-1}.
^1H NMR (D_2O, 400 MHz): δ 1.70 (m, 3H), 1.45 (m, 2H), 1.25 (m, 22H), 0.77 (t, 3H, J = 6.7 Hz) ppm.
Mass Spec. (FAB, + ions) m/e 525 (M + K), 487 (M + H), 469 (M-H_2O + H), 449 (M-K + 2H).

Anal. Calc'd for $C_{15}H_{31}O_5K_3P_2$ + 0.90 H_2O			
Found:	C, 35.82; C, 35.58;	H, 6.58; H, 6.95;	P, 12.32 P, 12.69.

The following compounds suitable for use in the method of the invention for inhibiting cholesterol biosynthesis by inhibiting de novo squalene production were prepared employing procedures similar to that described in Example 1;

heptylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or trisodium or tripotassium salt;

nonylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrasodium or tetrapotassium salt;

decylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrasodium or tetrapotassium salt;

tridecylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof;

octadecylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrasodium or tetrapotassium salt;

heneicosylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrasodium or tetrapotassium salt;

(6-methyl-5-heptenylidene)bisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrapotassium or tetrasodium salt;

[2-(4-butylphenyl)ethylidene]bisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof.

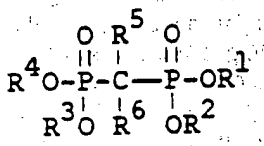
Claims

1. Use of a therapeutically effective amount of a bisphosphonate squalene synthetase inhibitor, wherein

the phosphonates are bridged by a methylene group, and which includes at least one lipophilic group attached to the methylene group, wherein the term "lipophilic group" refers to a group which contains at least six carbons and is required for strong enzyme inhibitor binding and inhibition of the enzyme squalene synthetase or other enzymes in the cholesterol biosynthetic pathway,

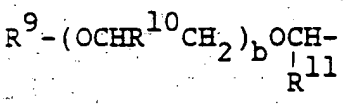
for the preparation of a pharmaceutical composition useful in inhibiting cholesterol biosynthesis or inhibiting or treating hypercholesterolemia and thereby inhibiting or treating atherosclerosis.

2. Use of a bisphosphonate compound having the structure

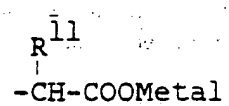


(I)

wherein R^1, R^2, R^3 and R^4 are the same or different and are H, alkyl, aryl, alkylaryl, arylalkyl, ammonium, alkali metal or a prodrug ester, wherein at least one of R^5 and R^6 is a hydrocarbyl group having at least 6 carbons (which is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, or arylalkenyl); heterocyclic (which is succinimdyl, pyridyl, quinalyl, morpholino, furanyl, indolyl, picolinyl, thiophene, imidazole, oxazole, isoxazole, thiazole, pyridine, 1,2,3-triazole, 1,2,4-triazole, benzimidazole, tetrahydrofuranyl, pyrrolidino, piperidino, 5-membered heteroarylmethyl containing 2 to 4 N atoms or 1-2 N atoms plus an O or S atom); heterocyclicalkyl (wherein heterocyclic is as defined above such as 1-(decahydroquinolin-3-yl)methane); amino; alkylamino; dialkylamino; arylalkylaminoalkyl; ethylcarbonyloxymethylamino; cycloalkyl(alkyl)amino; alkenylamino, cycloalkylamino, aminocycloalkyl; aminocycloalkylalkyl; N-hydroxy-N-ethylamino; acetylamino; aminoalkyloxyalkyl; (benzo- or cyclohexeno-fused) 5 membered heteroaryl containing 2-4 N atoms or 1-2 Natoms plus an O or S atom; R^8-X-$(CH_2)_a$- (wherein R^8 is H, alkyl, or a nitrogen containing 6-membered aromatic ring which is pyridyl, indanyl, hexahydroindanyl or picolyl; X is O, NH or a single bond and a is 0 to 7);



(wherein R^9 is C_1-C_{10} alkyl, optionally substituted aryl, phenylalkyl or naphthylalkyl),



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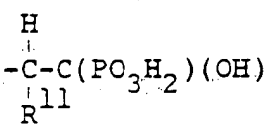
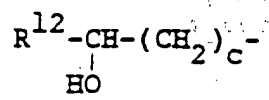
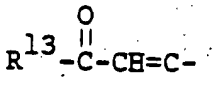


(wherein R^{10} and and R^{11} are the same or different and are H or methyl, b is 1 to 20));



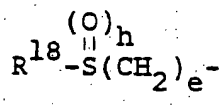
(wherein R^{12} is H, phenyl or phenyl substituted with halogen, alkyl or hydroxy and c is 0 to 9);



(wherein R^{13} is tert-alkyl ($CR^{14}R^{15}R^{16}$ wherein R^{14} and R^{15} are independently C_1-C_3 alkyl and R^{16} is C_1-C_{10} alkyl), cycloalkyl, aryl or heteroaryl, or substituted cycloalkyl, substituted aryl or substituted heteroaryl wherein the substituent is halogen, C_1-C_4 alkyl, alkoxy or dialkylamino);

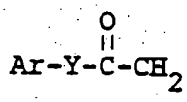
4-Cl-C_6H_5-S-CH_2; aryloxy;

R^{17}-$(QCH_2CH_2)_dO$- (wherein R^{17} is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, aryl or arylalkyl, or each of the above R^{17} groups optionally substituted with C_1-C_4 alkyl, amino, alkylamino, carboxyl, alkoxycarbonyl, hydroxy, alkoxy, phenoxy, mercapto, alkylthio, phenylthio, halogen or trifluoromethyl, Q is O or S and d is 0, 1 or 2);



(wherein e is 0 to 10, h is 0, 1 or 2, R^{18} is H, cycloalkyl, aryl, alkyl, each optionally substituted with OH, SH, halogen, alkoxycarbonyl or NZ_1Z_2, phenyl optionally substituted with halogen, nitro, lower alkyl, alkoxy, trifluoromethyl, amino, carboxyl, CO_2alkyl, -$CONZ_1Z_2$, -$CSNZ_1Z_2$, a 5- or 6-membered heterocyclic radical containing 1 or 2 heteroatoms, which are N or S, which may or may not be fused to a benzene ring, Z_1 and Z_2 are independently H or lower alkyl);

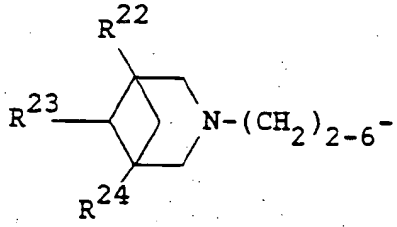
thiol; phenylthio; chlorophenylthio; 4-thiomorpholinyl;



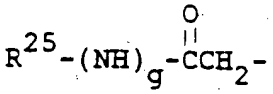
(wherein Ar is aryl, pyrrolyl or aryl optionally substituted with C_1-C_4 alkyl, alkoxy, halo (F, Cl), naphthyl, biphenyl or thienyl and Y is NH or a single bond);

$R^{19}SCH_2$- (wherein R^{19} is alkyl, aryl or arylalkyl);

A-$(CH_2)_f$-NH- (wherein A is C_5-C_8 cycloalkenyl, bicycloheptyl, bicycloheptenyl, saturated C_4-C_7 heterocycle containing O,S,SO or SO_2);



(wherein R^{22} is H, C_1-C_{20} alkyl, alkoxy, aryl, R^{23} is H, C_1-C_{20} alkyl, alkoxy, aryl, halo, carboxyl, R^{24} is H, C_1-C_{20} alkyl, alkoxy);

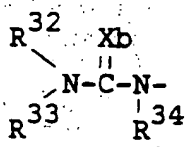


(wherein R^{25} is (alkyl-substituted)pyrrolyl or phenyl and g is 0 or 1);

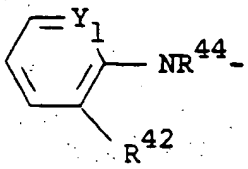
aromatic-substituted mono- or biazacyclylalkyl (alkyl group bonds with the N in the heterocycle) (such as 3-(4-phenylpiperidino)propyl);

R^{31}-Ax-CO-CH_2-

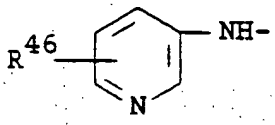
(wherein Ax is phenyl, naphthyl, mono- or bicyclic-N-containing heterocycle and R^{31} is H, halo, lower alkyl or lower alkoxy);



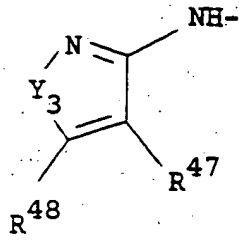
(wherein R^{32} is aryl, aralkyl, alkyl, R^{33} is H or aryl, Xb is O or S, and R^{34} is H or alkyl);



(wherein R^{42} is H, alkyl or halo, Y_1 is N, NO, or $NR^{43}Y_2$ wherein R^{43} is alkyl and Y_2 is halo; and R^{44} is H or aliphatic acyl);



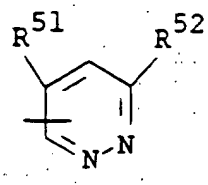
(wherein R^{46} is H, halo or alkyl);

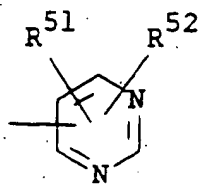


(wherein Y_3 is O or NH, R^{47} is H, alkyl or halo, and R^{48} is H or alkyl);

R^{50} -NH-

(wherein R^{50} is





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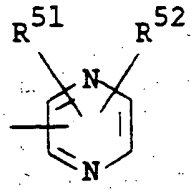
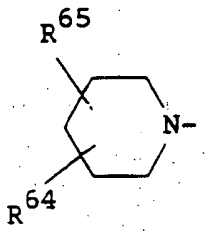
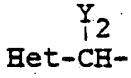


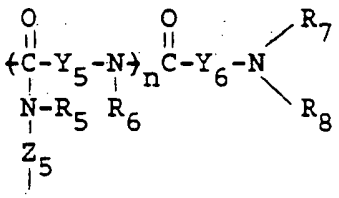
wherein R^{51} and R^{52} are H, halo, alkyl or hydroxy);



(wherein R^{64} is alkyl and R^{65} is H or alkyl;



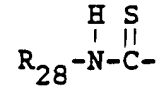
wherein Het is a heteroaromatic 5-membered ring with 2 or 3 heteroatoms, optionally partially hydrogenated and optionally substituted by one or more alkyl, alkoxy, phenyl, cyclohexyl, cyclohexylmethyl, halo or amino, with 2 adjacent alkyl optionally together forming a ring (Het cannot be pyrazole), and Y_2 is H or lower alkyl);



(wherein Y_4 is H or OH, R_5-R_8 are independently H or lower alkyl, whereby R_7 and Y_5 or R_6 and Y_5 or R_5 and Z_5, together with the nitrogen atom to which they are attached can form a 5- or 6-membered ring, Y_6 and Y_5 which can be the same or different are C_1-C_6 alkylene chains optionally substituted by aromatic or heteroaromatic radicals, Z_5 is C_1 to C_6 alkylene which can include heteroatoms and optionally substituted by aromatic or heteroaromatic, n is 0, 1 or 2;

R_{27}-Z_9-

(wherein R_{27} is aryl or heterocyclyl both optionally substituted by one or more of lower alkyl, lower alkoxy, lower alkylthio, halo(lower)alkyl, acyl, acylamino or halo, or R_{27} is lower alkyl substituted by heterocyclyl which is optionally substituted by acyl); R_{27}-Z_9 is R_{27}-NHC(=X_9), R_{27}-C(=O)NH-, R_{27}-SO_2-NH- (wherein X_9 is O or S);



(wherein R_{28} is phenyl, pyridyl or quinolyl substituted by lower alkylsulphonylamino, halo-lower alkylsulphonylamino, arylsulphonylamino and mono- or di-lower alkylamino);

R_{29}-CO-[-R_{30}(CH_2)$_o$CO-]$_p$-NH-

(wherein R_{29}-CO- is a residue of a pharmaceutically active compound R_{29}-COOH, wherein R_{29} is an anti-inflamatory agent, or antioncotic agent or hormone ,

R_{30} is -NH- or -O-

p is 0 or 1;

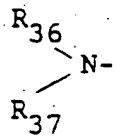
o is 1-10);

R_{33}-(CH_2)$_q$-

(wherein R_{33} is an N-bonded azabicycloalkyl group with 3 to 8-membered rings and q is 2 to 4);

R_{34}-(CH_2)$_r$-

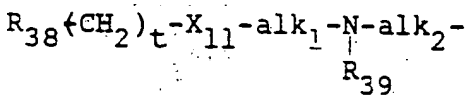
(wherein R_{34} is an N-bonded, aryl-substituted mono- or diazacycloaliphatic group);



(wherein R_{36} is 5 membered heteroaryl with 2-4 N or with 1-2 N plus an O or S atom, optionally fused to a benzo or cyclohexeno ring;

R_{36} can be C substituted by lower alkyl, phenyl (optionally substituted by lower alkyl, alkoxy and/or halo), lower alkoxy, OH, di(lower alkyl)amino, lower alkylthio and/or halo, and/or N substituted by lower alkyl or phenyl (lower) alkyl (optionally substituted by lower alkyl, lower alkoxy and/or halo);

R_{37} is H or lower alkyl; provided R_{37} is not H if R_{36} is optionally substituted alkyl and/or halo substituted 3-pyrazolyl or 3-isoxazolyl);

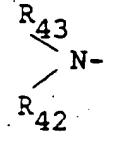


(wherein R_{38} is aromatic residue;

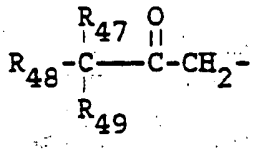
t is 0-3;

X_{11} is 0 S (optionally oxidized) or imino (optionally substituted by aliphatic group);

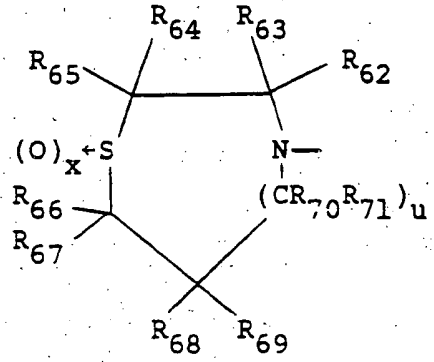
alk_1 and alk_2 are divalent aliphatic groups; R_{39} is H or monovalent aliphatic group);



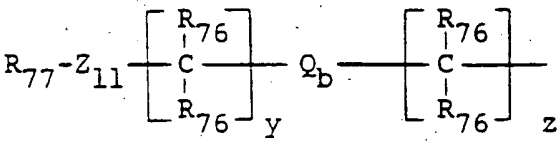
(wherein R_{42} and R_{43} are hydrogen, alkyl having one to 22 carbon atoms, cycloalkyl having five to six carbon atoms, phenyl alkylphenyl having seven to 18 carbon atoms, phenylalkyl having seven to 18 carbon atoms and together with the nitrogen atom, piperidino, pyrrolidino and morpholino);



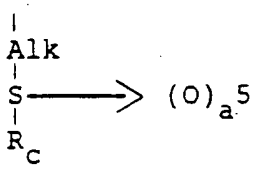
(wherein R_{47} is optionally branched C_1-C_8 alkyl,
R_{48} and R_{49} are each methyl or ethyl, and
M is H or a cation of a water-soluble base);



(wherein R_{62}-R_{71} is H, straight, branched or alicyclic 1-10C hydrocarbyl, aryl or aryl-(1-4C)-alkyl;
x is 0 or 1;
u is 0, 1 or 2;
or R_{62} and R_{64} may complete a 5- to 7-membered saturated aliphatic ring optionally substituted by 1 or more alkyl groups);



(wherein Z_{11} is an N-containing 6-membered ring heterocycle moiety selected from piperidinyl, diazinyl or triazinyl;
Q_b is a covalent bond, O, S or NR_{76};
y, z, and y + z are integers of 0-10;
R_{76} is H, or C_1-C_3 alkyl;
R_{77} is one or more substituted selected from H, halogen, 1-3C alkyl, unsubstituted amino and its amide derived from a 1-3C carboxylic acid, mono(1-3C alkyl) amino and its amide derived from a 1-3C carboxylic acid, di(1-3C alkyl)amino, tri(1-3C alkyl) ammonium, hydroxy or its ester derived from a 1-3C carboxylic acid, ether having 1-3C, CO_2H and its salts and esters derived from 1-3C alcohols, its amide optionally substituted with one or two 1-3C alkyl groups, and NO_2);



(wherein R_c represents:

C_1-C_6 alkyl group,

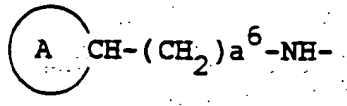
C_5-C_7 cycloalkyl group,

phenyl group optionally monosubstituted or polysubstituted by a halogen, a C_1-C_6 alkyl group or a trifluoromethyl group, or

5-membered or 6-membered heterocycle containing 1 or 2 heteroatoms chosen from nitrogen and sulfur,

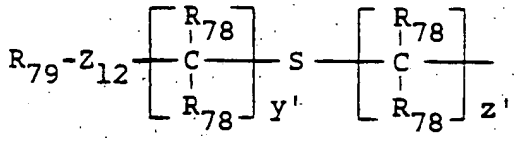
Alk denoted a linear or branched C_1-C_6 alkylene group,

a^5 represents 0 or the integer 1 or 2);



(wherein a^6 is 0 to 4 and

Ring A is 5-8C cycloalkenyl, bicycloheptyl, bicycloheptenyl or 4-7C saturated heterocyclyl containing 0, S, SO or SO_2);



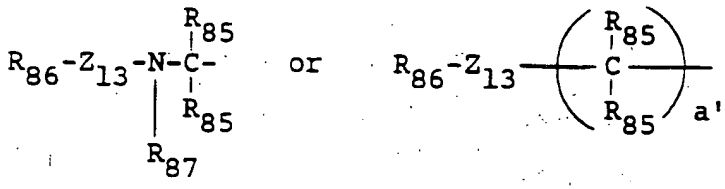
(wherein Z_{12} is a 6-membered aromatic ring containing ≥ 1 N atom(s); where:

the ring is optionally substituted by (optionally substituted, optionally unsaturated) 1-6C alkyl, (optionally substituted) aryl, (optionally substituted) benzyl, OH, halogen, carbonyl, alkoxy, NO_2, $CONH_2$, (optionally substituted) NH_2 and/or carboxylate, such as pyridine, pyridazine, pyrimidine or pyrazine ring;

R_{78} is H or (optionally substituted, optionally unsubstituted) 1-4C alkyl;

R_{79} is H, (optionally substituted, optionally unsubstituted) 1-6C alkyl, (optionally substituted) aryl, (optionally substituted) benzyl, OH, halogen, carbonyl, alkoxy, NO_2, $CONH_2$, (optionally substituted) amino or carboxylate,

y' + z' is 0 to 5);



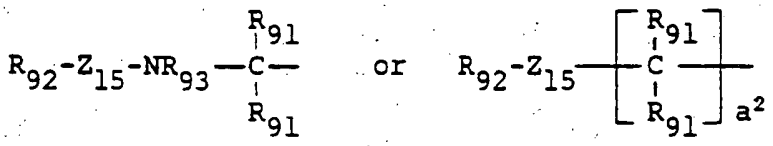
(wherein Z_{13} is a pyridine, pyridazine, pyrimidine or pyrazine ring, optionally substituted by optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, oxo, alkoxy, NO_2, amido, optionally substituted NH_2 or carboxylate;

R_{86} is H or optionally substituted, optionally unsaturated 1-4C alkyl;

R_{85} is one or more of H, optionally substituted, optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, oxo, alkoxy, NO_2, amido, optionally substituted NH_2 or carboxylate;

R_{87} is H, optionally substituted, optionally unsaturated 1-4C alkyl or acyl;

a' is 1-5);



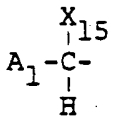
(wherein Z_{15} is a 6 membered aromatic ring containing one or more N atoms such as pyridine, pyridazine, pyrimidine or pyrazine, which ring may be substituted with one or more optionally substituted, optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, carbonyl, alkoxy, NO_2, amido, optionally substituted amino or carboxylate);

R_{91} is H or optionally substituted, optionally unsaturated 1-4C alkyl;

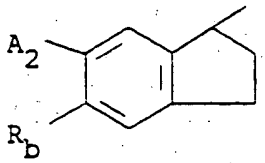
R_{92} is H or one or more substituents selected from optionally substituted, optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, carbonyl, alkoxy, NO_2, amido, optionally substituted amino or carboxylate;

R_{93} is H, optionally substituted, optionally unsaturated 1-4C alkyl or acyl;

a^2 is 1 to 5);



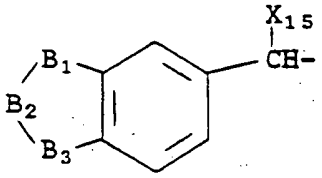
(wherein X_{15} is hydrogen, methyl, or ethyl, and A_1 is phenyl substituted in the para-position by isobutyl, cyclohexyl, alkoxy, or 1-pyrrolinyl and, optionally substituted additionally in the meta-position by fluorine or chlorine, or phenyl substituted in the meta-position by benzoyl or phenoxy, or phenyl substituted in the ortho-position by 2,4-dichlorophenoxy or 2,6-dichlorophenylamino);



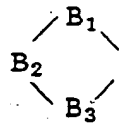
(wherein

R_b is cyclohexyl or cyclophenylmethyl; and

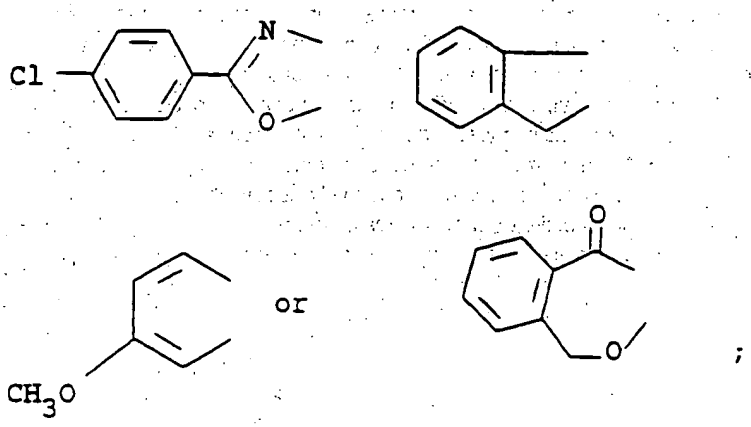
A_2 is hydrogen or chlorine);



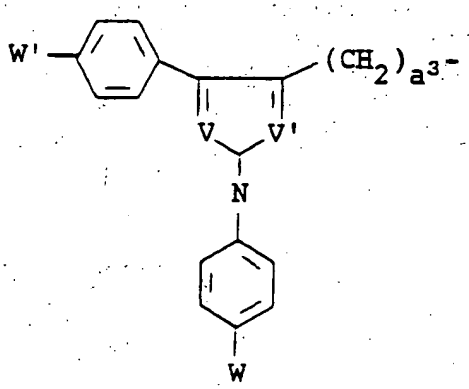
(wherein X_{15} is as defined above, and



is



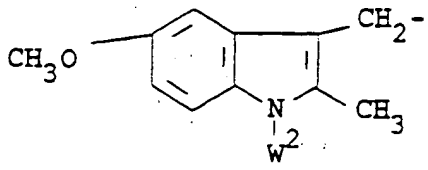
;



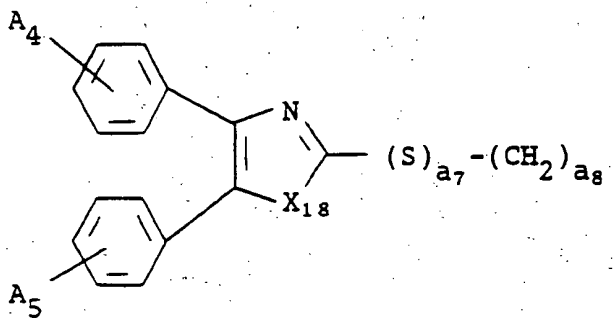
wherein a^3 is 1, 2 or 3;

W and W', are identical or different, and each is hydrogen, fluorine or chlorine, and

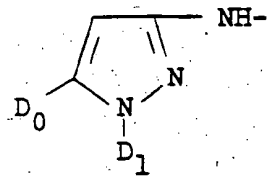
one of V and V' is nitrogen and the other is a methyne residue optionally substituted by a phenyl group, and



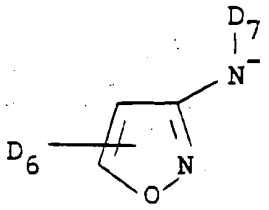
wherein W^2 is p-chlorobenzoyl or cinnamoyl);



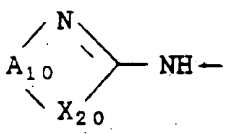
(wherein A_4 and A_5 are the same or different and are H, OH, lower alkoxy or halogen;
X_{15} is O, S or NH;
a_7 is 0 or 1;
a_8 is 0 or an integer of 1-6);



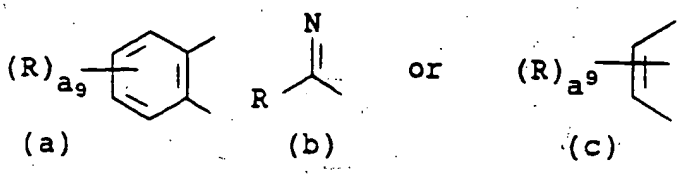
(wherein D_0 is H or alkyl;
D_1 is H or lower alkyl);



(wherein D_5 is H, 1-10C alkyl, 3-10C cycloalkyl, phenyl, 2-10C alkenyl (optionally substituted by phenyl) or phenyl(1-5C)alkyl (optionally ring-substituted by a 1-5C alkoxy);
D_7 is H or 2-6C alkanoyl);

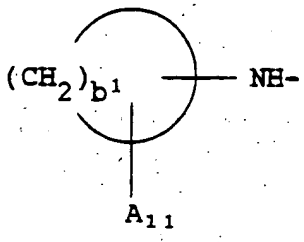


(wherein A_{10} is a group of formula (a)-(c):

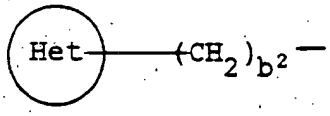


(a) (b) (c)

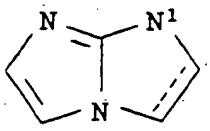
and X_{20} is O, S or NH);



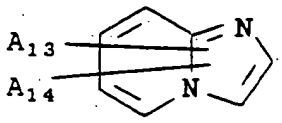
(wherein A_{11} is H or 1-5C alkyl; b_1 is 3-10);



(wherein ring Het is a group of formula (A) or (B):

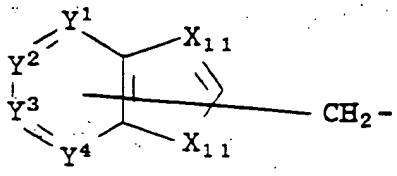


(A)



(B)

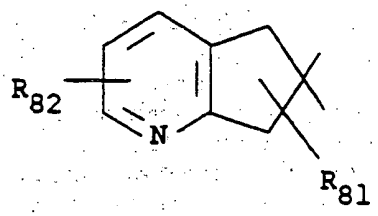
the dotted line represents an optional double bond; A_{13}, A_{14} are H, 1-5C alkyl, halogen or OH);

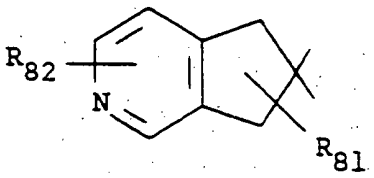


(wherein X_{11} are both N or one is N and the other is CH; one of Y^1-Y^4 is N and the rest is CH);

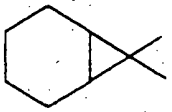
and the other of R^5 and R^6 is H, halogen, C_1-C_{30} alkyl, amino, alkylamino, dialkylamino, uriedo (NK_2CO-$N(R^{38})$- where R^{38} is H, alkyl, benzyl, phenyl optionally substituted with Cl or CH_3); alkenylamino, cycloalkylamino, aryloxy, pyridinium, guanidinium, ammonium, di-and tri-lower alkanolammonium, hydroxy, arylalkyl, alkoxy, alkylaryloxy, $-CH_2CO_2H$, $-CH_2PO_3H_2$, $-CH(PO_3H_2)(OH)$, $-CH_2CO_2C_2H_5$, $-CH_2CH(PO_3H_2)_2$, a hydrocarbyl radical as defined herein, a heterocyclic radical as defined herein, alkanoyl, an R^6 or R^5 radical as defined herein, a prodrug ester (such as (1-alkanoyloxy)alkyl, for example t-$C_4H_9CO_2CH_2$-, $CH_3CO_2CH_2$-);

at least one of R^5 and R^6 being a lipophilic group, or R^5 and R^6 can be joined to form a carbocyclic ring containing 3 to 12 carbons or a heterocyclic ring containing N, O and/or S atoms, such as of the formula





or



wherein R_{81} and R_{82} are each one or more substituents selected from H, optionally substituted saturated or unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, amido, OH, halogen, optionally substituted amino, amido, COOH, carbonyl, carboxylate, alkoxy and NO_2,

for the preparation of a pharmaceutical composition useful in inhibiting cholesterol biosynthesis or inhibiting or treating hypercholesterolemia and thereby inhibiting atherosclerosis.

3. Use according to Claim 1 or 2 wherein the squalene synthetase inhibitor employed is
tetramethyl 1(p-chlorophenyl)methane-1-hydroxy 1,1-diphosphonate,
tetramethyl 2,2-dimethyl 2-(p-chlorophenoxy)ethane 1-hydroxy-1,1-diphosphonate,
tetramethyl 1-[4(4'-chlorobenzoyl)phenyl]methane 1-hydroxy 1,1-diphosphonate,
dimethyl 1[(dimethoxyphosphinyl)p-chlorobenzyl]phosphate,
dimethyl [1(dimethoxyphosphinyl) 2,2-dimethyl 2-phenyl]-ethyl phosphate,
dimethyl [1(dimethoxyphosphinyl)2,2-dimethyl 2(p-chlorophenyl] ethyl phosphate,
tetramethyl 4-phenylbutylidene, 1,1-diphosphonate.

4. Use according to Claim 1 wherein the lipophilic group in the bisphosphonate compound is optionally substituted alkyl, optionally substituted alkenyl or optionally substituted aryl.

5. Use according to Claim 2 wherein the bisphosphonate is heptylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or trisodium or tripotassium salt;
nonylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrasodium or tetrapotassium salt;
decylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrasodium or tetrapotassium salt;
tridecylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof;
octadecylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrasodium or tetrapotassium salt;
heneicosylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrasodium or tetrapotassium salt;

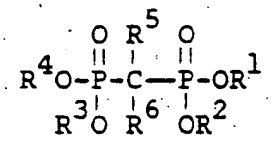
(6-methyl-5-heptenylidene)bisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrapotassium or tetrasodium salt;

[2-(4-butylphenyl)ethylidene]bisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof.

Claims for the following Contracting States : GR, ES

1. A method for the preparation of a pharmaceutical composition useful in inhibiting cholesterol biosynthesis or inhibiting or treating hypercholesterolemia and thereby inhibiting or treating atherosclerosis, which comprises combining a therapeutically effective amount of a bisphosphonate squalene synthetase inhibitor, wherein the phosphonates are bridged by a methylene group, and which includes at least one lipophilic group attached to the methylene group, wherein the term "lipophilic group" refers to a group which contains at least six carbons and is required for strong enzyme inhibitor binding and inhibition of the enzyme squalene synthetase or other enzymes in the cholesterol biosynthetic pathway, with a pharmaceutically acceptable carrier.

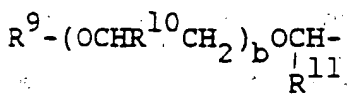
2. A method for the preparation of a pharmaceutical composition useful in inhibiting cholesterol biosynthesis or inhibiting or treating hypercholesterolemia and thereby inhibiting or treating atherosclerosis, which comprises combining a bisphosphonate compound having the structure



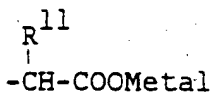
(I)

wherein R^1, R^2, R^3 and R^4 are the same or different and are H, alkyl, aryl, alkylaryl, arylalkyl, ammonium, alkali metal or a prodrug ester, wherein

at least one of R^5 and R^6 is a hydrocarbyl group having at least 6 carbons (which is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, or arylalkenyl); heterocyclic (which is succinimdyl, pyridyl, quinalyl, morpholino, furanyl, indolyl, picolinyl, thiophene, imidazole, oxazole, isoxazole, thiazole, pyridine, 1,2,3-triazole, 1,2,4-triazole, benzimidazole, tetrahydrofuranyl, pyrrolidino, piperidino, 5-membered heteroarylmethyl containing 2 to 4 N atoms or 1-2 N atoms plus an O or S atom); heterocyclicalkyl (wherein heterocyclic is as defined above such as 1-(decahydroquinolin-3-yl)methane); amino; alkylamino; dialkylamino; arylalkylaminoalkyl; ethylcarbonyloxymethylamino; cycloalkyl(alkyl)amino; alkenylamino, cycloalkylamino, aminocycloalkyl; aminocycloalkylalkyl; N-hydroxy-N-ethylamino; acetylamino; aminoalkyloxyalkyl; (benzo- or cyclohexeno-fused) 5 membered heteroaryl containing 2-4 N atoms or 1-2 Natoms plus an O or S atom; R^8-X-$(CH_2)_a$-(wherein R^8 is H, alkyl, or a nitrogen containing 6-membered aromatic ring which is pyridyl, indanyl, hexahydroindanyl or picolyl; X is O, NH or a single bond and a is 0 to 7);



(wherein R^9 is C_1-C_{10} alkyl, optionally substituted aryl, phenylalkyl or naphthylalkyl),



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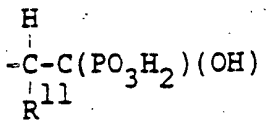
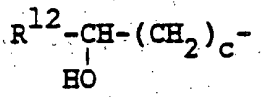
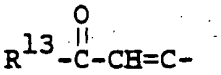


(wherein R^{10} and and R^{11} are the same or different and are H or methyl, b is 1 to 20));



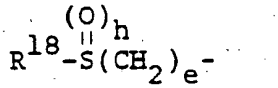
(wherein R^{12} is H, phenyl or phenyl substituted with halogen, alkyl or hydroxy and c is 0 to 9);



(wherein R^{13} is tert-alkyl ($CR^{14}R^{15}R^{16}$ wherein R^{14} and R^{15} are independently C_1-C_3 alkyl and R^{16} is C_1-C_{10} alkyl), cycloalkyl, aryl or heteroaryl, or substituted cycloalkyl, substituted aryl or substituted heteroaryl wherein the substituent is halogen, C_1-C_4 alkyl, alkoxy or dialkylamino);

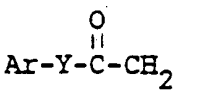
4-Cl-C_6H_5-S-CH_2; aryloxy;

R^{17}-$(QCH_2CH_2)_dO$- (wherein R^{17} is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, aryl or arylalkyl, or each of the above R^{17} groups optionally substituted with C_1-C_4 alkyl, amino, alkylamino, carboxyl, alkoxycarbonyl, hydroxy, alkoxy, phenoxy, mercapto, alkylthio, phenylthio, halogen or trifluoromethyl, Q is O or S and d is 0, 1 or 2);



(wherein e is 0 to 10, h is 0, 1 or 2, R^{18} is H, cycloalkyl, aryl, alkyl, each optionally substituted with OH, SH, halogen, alkoxycarbonyl or NZ_1Z_2, phenyl optionally substituted with halogen, nitro, lower alkyl, alkoxy, trifluoromethyl, amino, carboxyl, CO_2alkyl, $-CONZ_1Z_2$, $-CSNZ_1Z_2$, a 5- or 6-membered heterocyclic radical containing 1 or 2 heteroatoms, which are N or S, which may or may not be fused to a benzene ring, Z_1 and Z_2 are independently H or lower alkyl);

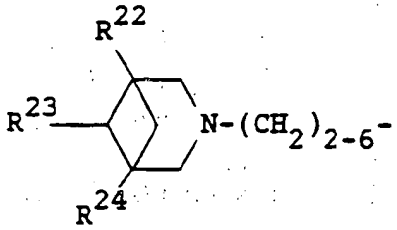
thiol; phenylthio; chlorophenylthio; 4-thiomorpholinyl;



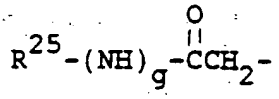
(wherein Ar is aryl, pyrrolyl or aryl optionally substituted with C_1-C_4 alkyl, alkoxy, halo (F, Cl), naphthyl, biphenyl or thienyl and Y is NH or a single bond);

$R^{19}SCH_2$- (wherein R^{19} is alkyl, aryl or arylalkyl);

A-$(CH_2)_f$-NH- (wherein A is C_5-C_8 cycloalkenyl, bicycloheptyl, bicycloheptenyl, saturated C_4-C_7 heterocycle containing O,S,SO or SO_2);



(wherein R^{22} is H, C_1-C_{20}alkyl, alkoxy, aryl, R^{23} is H, C_1-C_{20}alkyl, alkoxy, aryl, halo, carboxyl, R^{24} is H, C_1-C_{20} alkyl, alkoxy);

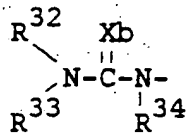


(wherein R^{25} is (alkyl-substituted)pyrrolyl or phenyl and g is 0 or 1);

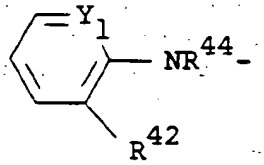
aromatic-substituted mono- or biazacyclylalkyl (alkyl group bonds with the N in the heterocycle) (such as 3-(4-phenylpiperidino)propyl);

R^{31}-Ax-CO-CH_2-

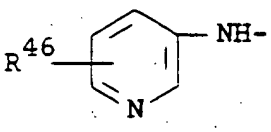
(wherein Ax is phenyl, naphthyl, mono- or bicyclic-N-containing heterocycle and R^{31} is H, halo, lower alkyl or lower alkoxy);



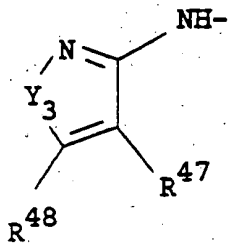
(wherein R^{32} is aryl, aralkyl, alkyl, R^{33} is H or aryl, Xb is O or S, and R^{34} is H or alkyl);



(wherein R^{42} is H, alkyl or halo, Y_1 is N, NO, or $NR^{43}Y_2$ wherein R^{43} is alkyl and Y_2 is halo; and R^{44} is H or aliphatic acyl);



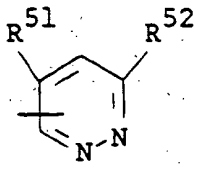
(wherein R^{46} is H, halo or alkyl);

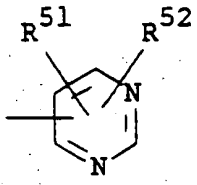


(wherein Y_3 is O or NH, R^{47} is H, alkyl or halo, and R^{48} is H or alkyl);

R^{50} -NH-

(wherein R^{50} is





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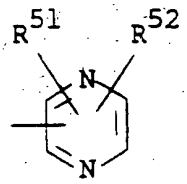
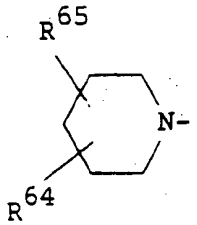
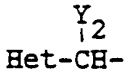


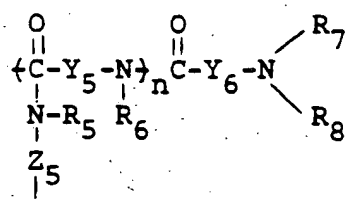
wherein R^{51} and R^{52} are H, halo, alkyl or hydroxy);



(wherein R^{64} is alkyl and R^{65} is H or alkyl;



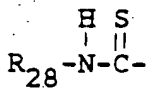
wherein Het is a heteroaromatic 5-membered ring with 2 or 3 heteroatoms, optionally partially hydrogenated and optionally substituted by one or more alkyl, alkoxy, phenyl, cyclohexyl, cyclohexylmethyl, halo or amino, with 2 adjacent alkyl optionally together forming a ring (Het cannot be pyrazole), and Y_2 is H or lower alkyl);



(wherein Y_4 is H or OH, R_5-R_8 are independently H or lower alkyl, whereby R_7 and Y_6 or R_6 and Y_5 or R_5 and Z_5, together with the nitrogen atom to which they are attached can form a 5- or 6-membered ring, Y_6 and Y_5 which can be the same or different are C_1-C_6 alkylene chains optionally substituted by aromatic or heteroaromatic radicals, Z_5 is C_1 to C_6 alkylene which can include heteroatoms and optionally substituted by aromatic or heteroaromatic, n is 0, 1 or 2;

R_{27}-Z_9-

(wherein R_{27} is aryl or heterocyclyl both optionally substituted by one or more of lower alkyl, lower alkoxy, lower alkylthio, halo(lower)alkyl, acyl, acylamino or halo, or R_{27} is lower alkyl substituted by heterocyclyl which is optionally substituted by acyl); R_{27}-Z_9 is R_{27}-NHC(=X_9), R_{27}-C(=O)NH-, R_{27}-SO_2-NH- (wherein X_9 is O or S);



(wherein R_{28} is phenyl, pyridyl or quinolyl substituted by lower alkylsulphonylamino, halo-lower alkylsulphonylamino, arylsulphonylamino and mono- or di-lower alkylamino);

R_{29}-CO-[-$R_{30}(CH_2)_oCO$-]$_p$-NH-

(wherein R_{29}-CO- is a residue of a pharmaceutically active compound R_{29}-COOH, wherein R_{29} is an anti-inflamatory agent, or antioncotic agent or hormone ,

R_{30} is -NH- or -O-

p is 0 or 1;

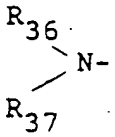
o is 1-10);

R_{33}-$(CH_2)_q$-

(wherein R_{33} is an N-bonded azabicycloalkyl group with 3 to 8-membered rings and q is 2 to 4);

R_{34}-$(CH_2)_r$-

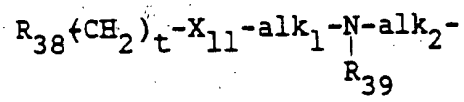
(wherein R_{34} is an N-bonded, aryl-substituted mono- or diazacycloaliphatic group);



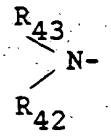
(wherein R_{36} is 5 membered heteroaryl with 2-4 N or with 1-2 N plus an O or S atom, optionally fused to a benzo or cyclohexeno ring;

R_{36} can be C substituted by lower alkyl, phenyl (optionally substituted by lower alkyl, alkoxy and/or halo), lower alkoxy, OH, di(lower alkyl)amino, lower alkylthio and/or halo, and/or N substituted by lower alkyl or phenyl (lower) alkyl (optionally substituted by lower alkyl, lower alkoxy and/or halo);

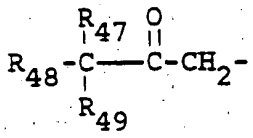
R_{37} is H or lower alkyl; provided R_{37} is not H if R_{36} is optionally substituted alkyl and/or halo substituted 3-pyrazolyl or 3-isoxazolyl);



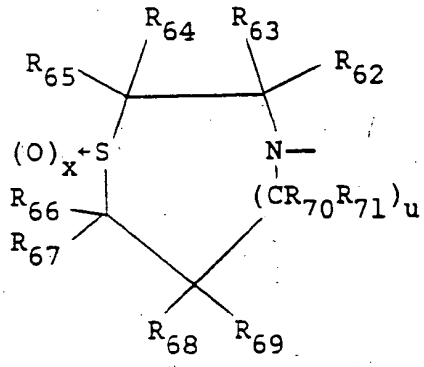
(wherein R_{38} is aromatic residue;
t is 0-3;
X_{11} is O S (optionally oxidized) or imino (optionally substituted by aliphatic group);
alk_1 and alk_2 are divalent aliphatic groups; R_{39} is H or monovalent aliphatic group);



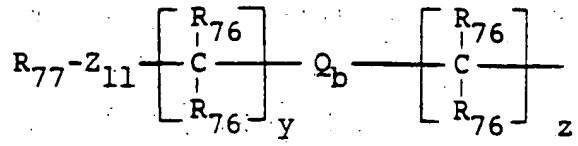
(wherein R_{42} and R_{43} are hydrogen, alkyl having one to 22 carbon atoms, cycloalkyl having five to six carbon atoms, phenyl alkylphenyl having seven to 18 carbon atoms, phenylalkyl having seven to 18 carbon atoms and together with the nitrogen atom, piperidino, pyrrolidino and morpholino);



(wherein R_{47} is optionally branched C_1-C_8 alkyl,
R_{48} and R_{49} are each methyl or ethyl, and
M is H or a cation of a water-soluble base);



(wherein R_{62}-R_{71} is H, straight, branched or alicyclic 1-10C hydrocarbyl, aryl or aryl-(1-4C)-alkyl;
x is 0 or 1;
u is 0, 1 or 2;
or R_{62} and R_{64} may complete a 5- to 7-membered saturated aliphatic ring optionally substituted by 1 or more alkyl groups);



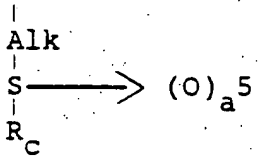
(wherein Z_{11} is an N-containing 6-membered ring heterocycle moiety selected from piperidinyl, diazinyl or triazinyl;

Q_b is a covalent bond, O, S or NR_{76};

y, z, and y + z are integers of 0-10;

R_{76} is H, or C_1-C_3alkyl;

R_{77} is one or more substituted selected from H, halogen, 1-3C alkyl, unsubstituted amino and its amide derived from a 1-3C carboxylic acid, mono(1-3C alkyl) amino and its amide derived from a 1-3C carboxylic acid, di(1-3C alkyl)amino, tri(1-3C alkyl) ammonium, hydroxy or its ester derived from a 1-3C carboxylic acid, ether having 1-3C, CO_2H and its salts and esters derived from 1-3C alcohols, its amide optionally substituted with one or two 1-3C alkyl groups, and NO_2);



(wherein R_c represents:

C_1-C_6 alkyl group,

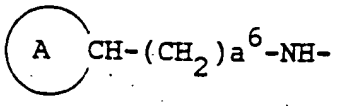
C_5-C_7 cycloalkyl group,

phenyl group optionally monosubstituted or polysubstituted by a halogen, a C_1-C_6 alkyl group or a trifluoromethyl group, or

5-membered or 6-membered heterocycle containing 1 or 2 heteroatoms chosen from nitrogen and sulfur,

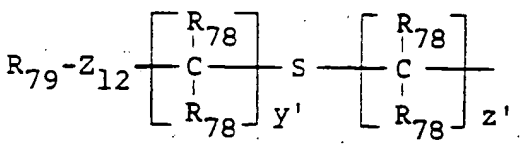
Alk denoted a linear or branched C_1-C_6 alkylene group,

a^5 represents 0 or the integer 1 or 2);



(wherein a^5 is 0 to 4 and

Ring A is 5-8C cycloalkenyl, bicycloheptyl, bicycloheptenyl or 4-7C saturated heterocyclyl containing 0, S, SO or SO_2);



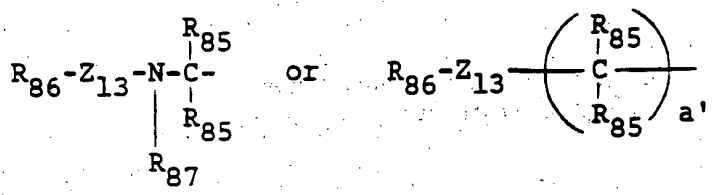
(wherein Z_{12} is a 6-membered aromatic ring containing ≥ 1 N atom(s); where:

the ring is optionally substituted by (optionally substituted, optionally unsaturated) 1-6C alkyl, (optionally substituted) aryl, (optionally substituted) benzyl, OH, halogen, carbonyl, alkoxy, NO_2, $CONH_2$, (optionally substituted) NH_2 and/or carboxylate, such as pyridine, pyridazine, pyrimidine or pyrazine ring;

R_{78} is H or (optionally substituted, optionally unsubstituted) 1-4C alkyl;

R_{79} is H, (optionally substituted, optionally unsubstituted) 1-6C alkyl, (optionally substituted) aryl, (optionally substituted) benzyl, OH, halogen, carbonyl, alkoxy, NO_2, $CONH_2$, (optionally substituted) amino or carboxylate,

y' + z' is 0 to 5);



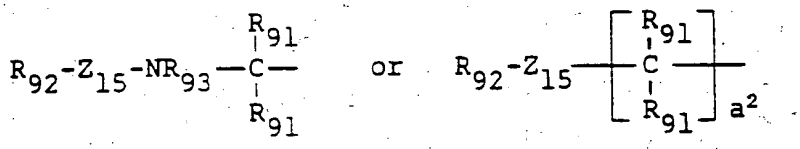
(wherein Z_{13} is a pyridine, pyridazine, pyrimidine or pyrazine ring, optionally substituted by optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, oxo, alkoxy, NO_2, amido, optionally substituted NH_2 or carboxylate;

R_{86} is H or optionally substituted, optionally unsaturated 1-4C alkyl;

R_{86} is one or more of H, optionally substituted, optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, oxo, alkoxy, NO_2, amido, optionally substituted NH_2 or carboxylate;

R_{87} is H, optionally substituted, optionally unsaturated 1-4C alkyl or acyl;

a' is 1-5);



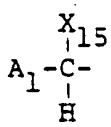
(wherein Z_{15} is a 6 membered aromatic ring containing one or more N atoms such as pyridine, pyridazine, pyrimidine or pyrazine, which ring may be substituted with one or more optionally substituted, optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, carbonyl, alkoxy, NO_2, amido, optionally substituted amino or carboxylate);

R_{91} is H or optionally substituted, optionally unsaturated 1-4C alkyl;

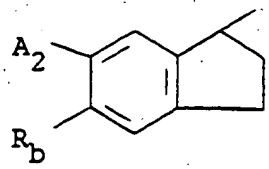
R_{92} is H or one or more substituents selected from optionally substituted, optionally unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, OH, halogen, carbonyl, alkoxy, NO_2, amido, optionally substituted amino or carboxylate;

R_{93} is H, optionally substituted, optionally unsaturated 1-4C alkyl or acyl;

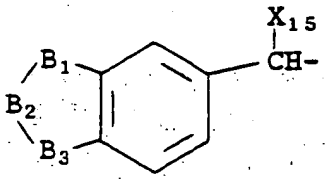
a^2 is 1 to 5);



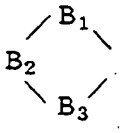
(wherein X_{15} is hydrogen, methyl, or ethyl, and A_1 is phenyl substituted in the para-position by isobutyl, cyclohexyl, alkoxy, or 1-pyrrolinyl and, optionally substituted additionally in the meta-position by fluorine or chlorine, or phenyl substituted in the meta-position by benzoyl or phenoxy, or phenyl substituted in the ortho-position by 2,4-dichlorophenoxy or 2,6-dichlorophenylamino);



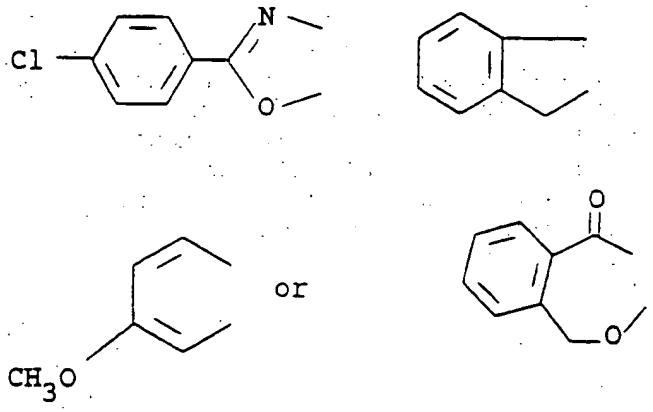
(wherein
R_b is cyclohexyl or cyclophenylmethyl; and
A_2 is hydrogen or chlorine);



(wherein X_{15} is as defined above, and



is



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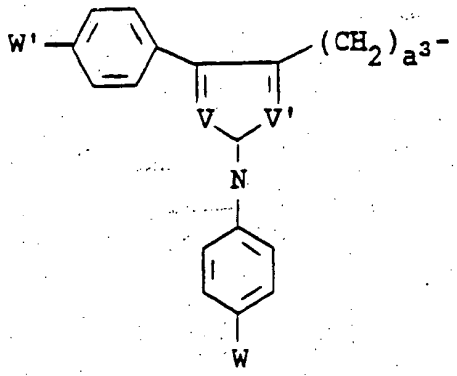
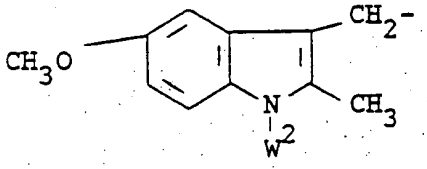
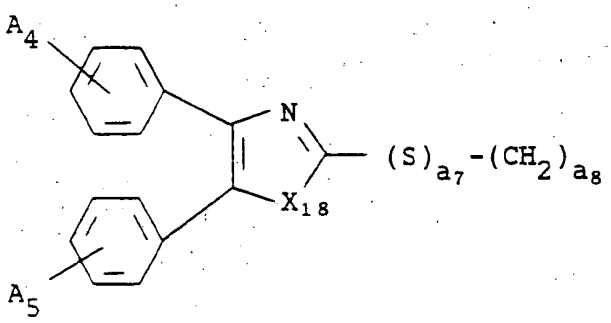


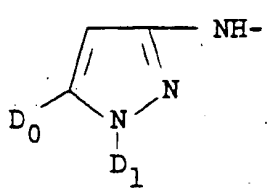
wherein a^3 is 1, 2 or 3;
W and W', are identical or different, and each is hydrogen, fluorine or chlorine, and
one of V and V' is nitrogen and the other is a methyne residue optionally substituted by a phenyl group, and



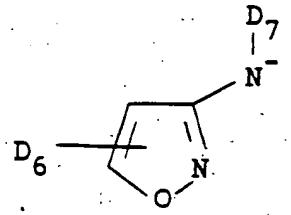
wherein W^2 is p-chlorobenzoyl or cinnamoyl);



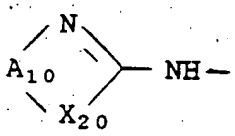
(wherein A_4 and A_5 are the same or different and are H, OH, lower alkoxy or halogen;
X_{15} is O, S or NH;
a_7 is 0 or 1;
a_8 is 0 or an integer of 1-6);



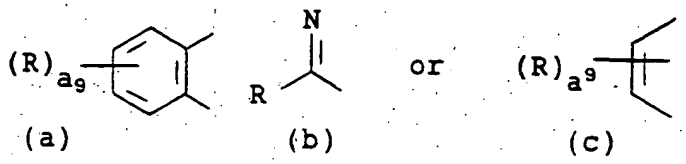
(wherein D_0 is H or alkyl;
D_1 is H or lower alkyl);



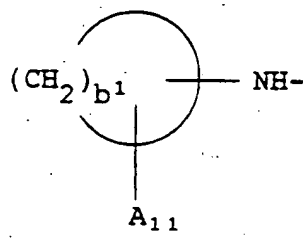
(wherein D_6 is H, 1-10C alkyl, 3-10C cycloalkyl, phenyl, 2-10C alkenyl (optionally substituted by phenyl) or phenyl(1-5C)alkyl (optionally ring-substituted by a 1-5C alkoxy);
D_7 is H or 2-6C alkanoyl);



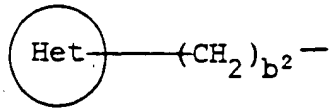
(wherein A_{10} is a group of formula (a)-(c):



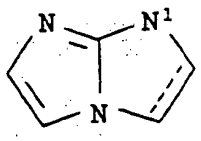
and X_{20} is O, S or NH);



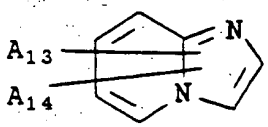
(wherein A_{11} is H or 1-5C alkyl; b_1 is 3-10);



(wherein ring Het is a group of formula (A) or (B):

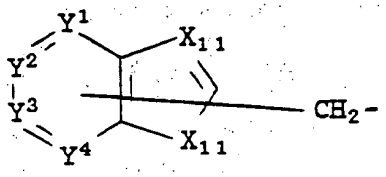


(A)



(B)

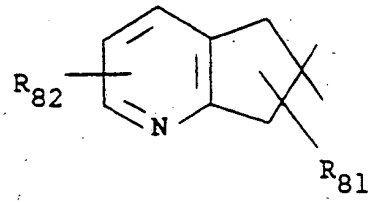
the dotted line represents an optional double bond; A_{13}, A_{14} are H, 1-5C alkyl, halogen or OH);

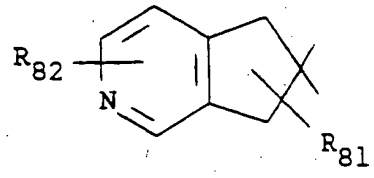


(wherein X_{11} are both N or one is N and the other is CH; one of Y^1-Y^4 is N and the rest is CH);

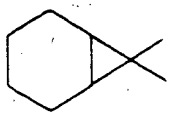
and the other of R^5 and R^6 is H, halogen, C_1-C_{30} alkyl, amino, alkylamino, dialkylamino, uriedo (NH_2CO-$N(R^{38})$- where R^{38} is H, alkyl, benzyl, phenyl optionally substituted with Cl or CH_3); alkenylamino, cycloalkylamino, aryloxy, pyridinium, guanidinium, ammonium, di-and tri-lower alkanolammonium, hydroxy, arylalkyl, alkoxy, alkylaryloxy, $-CH_2CO_2H$, $-CH_2PO_3H_2$, $-CH(PO_3H_2)(OH)$, $-CH_2CO_2C_2H_5$, $-CH_2CH(PO_3H_2)_2$, a hydrocarbyl radical as defined herein, a heterocyclic radical as defined herein, alkanoyl, an R^6 or R^5 radical as defined herein, a prodrug ester (such as (1-alkanoyloxy)alkyl, for example t-$C_4H_9CO_2CH_2$-, $CH_3CO_2CH_2$-);

at least one of R^5 and R^6 being a lipophilic group, or R^5 and R^6 can be joined to form a carbocyclic ring containing 3 to 12 carbons or a heterocyclic ring containing N, O and/or S atoms, such as of the formula





or



wherein R_{s1} and R_{s2} are each one or more substituents selected from H, optionally substituted saturated or unsaturated 1-6C alkyl, optionally substituted aryl, optionally substituted benzyl, amido, OH, halogen, optionally substituted amino, amido, COOH, carbonyl, carboxylate, alkoxy and NO_2,

with a pharmaceutically acceptable carrier.

3. The method as defined in Claim 1 or 2 wherein the squalene synthetase inhibitor employed is
tetramethyl 1(p-chlorophenyl)methane-1-hydroxy 1,1-diphosphonate,
tetramethyl 2,2-dimethyl 2-(p-chlorophenoxy)ethane 1-hydroxy-1,1-diphosphonate,
tetramethyl 1-[4(4'-chlorobenzoyl)phenyl]methane 1-hydroxy 1,1-diphosphonate,
dimethyl 1[(dimethoxyphosphinyl)p-chlorobenzyl]phosphate,
dimethyl [1(dimethoxyphosphinyl) 2,2-dimethyl 2-phenyl]-ethyl phosphate,
dimethyl [1(dimethoxyphosphinyl)2,2-dimethyl 2(p-chlorophenyl] ethyl phosphate,
tetramethyl 4-phenylbutylidene, 1,1-diphosphonate.

4. The method as defined in Claim 1 wherein the lipophilic group is optionally substituted alkyl, optionally substituted alkenyl or optionally substituted aryl.

5. The method as defined in Claim 2 wherein the bisphosphonate is heptylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or trisodium or tripotassium salt;
nonylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrasodium or tetrapotassium salt;
decylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrasodium or tetrapotassium salt;
tridecylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof;
octadecylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrasodium or tetrapotassium salt;
heneicosylidenebisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrasodium or tetrapotassium salt;
(6-methyl-5-heptenylidene)bisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof, or tetrapotassium or tetrasodium salt;
[2-(4-butylphenyl)ethylidene]bisphosphonic acid, esters thereof, salts thereof, or mixed ester-salts thereof.